Appendix A: Participants List

WORKING GROUP MEMBERS

Lionel Bascles, PhD, *Senior VP, Global Head of Clinical Sciences & Operations, Sanofi*

Myron Cohen, MD, *Associate Vice Chancellor for Global Health and Medical Affairs, Director, Institute for Global Health & Infectious Diseases, University of North Carolina Chapel Hill*

Victoria Davey, PhD, MPH, *U.S. Department of Veterans Affairs*

Elizabeth Desrosiers (Co-Chair), MS, PMP, *Executive Director, Clinical Sciences and Study Management, Merck*

James Dickens, *Program Manager, National Center for Advancing Translational Sciences (NCATS)*

David Goff, MD, PhD, *Director, Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute (NHLBI)*

Michael Kurilla (Co-Chair), MD, PhD, *Director – Division of Clinical Innovation, National Center for Advancing Translational Sciences (NCATS)*

George Mensah, MD, *Director, Center for Translation Research & Implementation Science, National Heart, Lung, and Blood Institute (NHLBI)*

Seema Nayak, MD, *Director, Office of Clinical Research Resources, National Institute of Allergy and Infectious Diseases (NIAID)*

Manizhe Payton, MPH, *Director, Office of Clinical Site Oversight, NIAID*

Laura Resnansky, *Vice President, Global Head of Clinical Operations – Immunology, Infectious Diseases, Ophthalmology and Neuroscience, Genentech*

Christine Sizemore, PhD, *Director, International Relations, Fogarty International Center*

Michael Vincent, MD, PhD, *Senior Vice President, Chief Scientific Officer of Inflammation and Immunology Research and Development, Pfizer*

Gail Weinmann, MD, *Deputy Director, Division of Lung Diseases, NHLBI*

INVITED PARTICIPANTS

Francis Collins, MD, PhD, *Director, NIH*

Michelle Culp, *Office of Science Policy, NIH*

Ellen Gadbois, PhD, *Program Lead, Emerging Biotechnology Policy, NIH Office of Science Policy*

Penny Heaton, MD, *Chief Executive Officer, Bill & Melinda Gates Medical Research Institute*

Dermot Kenny, *Global Head of Data Operations, Novartis*

Ashley Parker, PhD, *Health Science Policy Analyst, NIH*

FNIH STAFF

Stephanie James, PhD, *Senior VP of Science, Foundation for the National Institutes of Health*

(FNIH)
Michael Santos, PhD, *Associate VP of Science, FNIH*
Karen H. Tountas, PhD, *Scientific Program Manager, Science*
David Wholley, MPhil, *Senior VP of Research Partnerships, FNIH*

Tanvir Ahmed, *Senior Consultant, Deloitte*
Kevin Footer, MBA, *Senior Manager, Deloitte*
Ethan Jones, *Business Technology Analyst, Deloitte*
Alyssa Long, *Manager, Deloitte*
Jonathan Wachtel, MBA, *Manager, Deloitte*

Bethany Stokes, MS, *Writer, Rose Li and Associates, Inc.*

High-Level Meeting Summary

The Preclinical Working Group (WG) discussed choosing a SARS-CoV-2 reference strain for therapeutics testing; testing therapeutic combinations against COVID-19; prioritizing NHPs for therapeutics testing; and monitoring SARS-CoV-2 genetic changes to inform compound prioritization.

Action Items

- Dr. Joe Menetski will assemble a NHP Study Prioritization Subgroup and begin drafting a list of information required from sponsors to inform the prioritization
- Dr. Colvis will arrange a combination therapy meeting and invite several members of the TX-Clinical WG (Drs. Kara Carter, Tomas Cihlar, Michael Diamond, Josh Fessel, Jay Grobler, and Yuao Zhu)
- The *In Vivo* Subgroup will discuss during its next meeting how to incorporate genotype monitoring into ACTIV's remits

SARS-CoV-2 Reference Strain

Two SARS-CoV-2 strains are currently under consideration to be reference strains for *in vitro* assays and animal model testing: (1) the widely available and well-known Seattle strain and (2) the currently most prevalent infectious strain that contains a D614G-mutation strain (both can be supplied by (b)(4) . The WG agreed that two reference strains would ensure strong validation of treatment agents and allow scientists to better understand how the D614G mutation changes COVID-19 pathology compared to non-mutated SARS-CoV-2 strains. However, using two reference strains could double testing requirements and therefore demand more resources.

To leverage any potential insights gained by studying the D614G mutation, the WG suggested that initially both the Seattle strain and a D614G mutated strain be used for *in vitro* model validation (e.g. conducting CPE and viral load assays). To conserve resources, bridging studies should be done so that previous results from the Seattle strain in small animal and NHP models can be compared to the new strain. The WG has decided that both strains would be produced as reference strains and comparative research would be encouraged with both. In addition, any agent that shows promising results, regardless of model, should be validated using a panel of 5-10 regional SARS-CoV-2 strains to help identify agents that will be effective against virus strains globally.

COVID-19 Combination Therapies

The WG will assist NCATS in submitting a proposal (b)(5) NCATS has shown preliminary (b)(5) The WG supports (b)(5) in the NCATS library.

The goal is to focus on combinations that demonstrate efficacy in vitro and could initiate clinical trials before 2021. Drs. Kara Carter, Tomas Cihlar, Michael Diamond, Josh Fessel, Jay Grobler, and Yuao Zhu will hold a meeting to discuss logistics of selecting compounds and determining testing criteria. Dr. Colvis will arrange a combination therapy meeting this week and invite several members of the TX-Clinical WG.

NHP Prioritization

The NIH Office of Research Infrastructure Programs (ORIP) has identified requests from (b)(4) NIAID, OWS, and others to use NHPs. To conserve limited NHP resources, the WG will establish a Prioritization Subgroup to rank these requests to access NHPs; studies poised to make an immediate impact on the course of the pandemic will be identified. This Subgroup will consider aspects such as quality of agents tested, time to complete each study, routes of viral infection, viral strain used, and NHP population used (e.g., in terms of age and comorbidities). The resulting list will then be used by NIH and the NPRCs to determine which NHP studies could have immediate impact on clinical outcomes.

Drs. James Anderson and Nancy Haigwood also noted that although NHPs from the Office of AIDS Research (OAR) have been approved for use in COVID-19 studies, NHPs will still be in short supply and therefore non-COVID-19 researche may be delayed. Using formal criteria to prioritize studies will help to ensure that these NHPs are repurposed appropriately It may be feasible to develop study paradigms allowing some NHPs to be used across multiple studies.

Dr. Joe Menetski will assemble a Prioritization Subgroup and begin drafting a list of information required from sponsors to inform the Subgroup's study rankings. The Subgroup will include Drs. Haigwood and Rappaport, several members of the TX-Clinical WG, and others.

Genotype Monitoring

Dr. Cihlar informed the WG that Gilead has been continually monitoring research literature to track genetic changes and genetic stability of SARS-CoV-2 and offered to provide the WG access to Gilead's monitoring system. Continuous genetic monitoring of specific genes important for SARS-CoV-2 activity may be used to predict the functional consequences of genetic mutations and provide ACTIV's Preclinical and TX Clinical WGs information to help prioritize therapeutics.

Other researchers tracking SARS-CoV-2 genetic changes, such as Marco Salemi at the University of Florida, may be able to contribute additional information. The *In Vivo* Subgroup will discuss during its next meeting if and how to incorporate genotype monitoring into ACTIV's remits.

Next Steps

Dr. Menetski will schedule a Combination Therapy Subgroup meeting and work with Drs. Sheri Hild and Rosa Maria Alvarez to draft the list of information needed for NHP study prioritization.

Appendix A: Participants List

WORKING GROUP MEMBERS

Peter Adams, PhD, (not in attendance) *Health Scientist, Project Officer, BARDA*

Annaliesa Anderson, PhD, (not in attendance) *Vice President and CSO Bacterial Vaccines, Pfizer*

Ralph Baric Professor, PhD, *Dept. of Epidemiology and Dept. of Micobiology and Immunology, UNC Chapel Hill*

Kara Carter, PhD, *Senior Vice President Infectious Disease, Evotec*

Marc Charette, PhD, *Division of Cardiovascular Diseases NIH, NHLBI*

Tomas Cihlar, PhD, *VP, and Head of Virology, Gilead*

Christine Colvis, PhD, *Director, Drug Development Partnership Programs, NCATS*

Damon Deming, PhD, *Virologist, Division of Antiviral Products, Office of New Drugs, FDA*

Michael Diamond, MD, PhD, *Professor, Depts. of Medicine, Molecular Microbiology, Pathology & Immunology, Washington University*

Ken Duncan, PhD, (not in attendance) *Gates Foundation*

Prabhavathi Fernandes, PhD, *Retired, most recently led biotechs Cempra and DarPharma*

Josh Fessel, MD, PhD, *Division of Lung Diseases NIH, NHLBI*

Clint Florence, PhD, *Program Officer, Research Resource Section, OBRR, DMID, NIAID*

Greg Gatto, PhD, *Drug Development Regulatory Project Leader, RTI*

Jay Grobler, PhD, *Director, Infectious Disease Biology, Merck*

Nancy Haigwood, PhD, *Director and Professor, Oregon National Primate Research Center, OHSU*

Judith Hewitt, PhD, *Deputy Director, Office of Biodefense, Research Resources and Translational Research, NIAID*

Samantha Jonson, MPS, *Special Assistant to the Director, NCATS*

Cat Lutz, PhD, *Senior Director, Mouse Repository & In Vivo Pharmacology, Rare and Orphan Disease Center, Jackson Laboratory*

Frank Nestle, MD, (not in attendance) *Global Head of Immunology Therapeutic Research Area and Chief Scientific Officer North America, Sanofi*

Liz Ottinger, PhD, (not in attendance) *Project Manager, NCATS*

David Payne, PhD, DSc, (not in attendance) *Vice President & Head, Medicine Opportunities Research Unit, GSK*

Louise Pitt, PhD, *Director, Center for Aerobiological Sciences, USAMRIID*

Tony Punturieri, MD, PhD, (not in attendance) *Division of Lung Diseases NIH, NHLBI*

Srinivas Rao, MBA, PhD, *Global Head Translational In Vivo Models, Sanofi*

Jay Rappaport, PhD, *Director and Chief Academic Officer, Tulane Primate Center*

John Young, PhD, *Global Head Infectious Diseases and Vice President, Roche*

INVITED PARTICIPANTS

James M. Anderson, M.D., Ph.D., Deputy Director for Program Coordination, Planning, and Strategic Initiatives, NIH

Ellen Gadbois, *Program Lead, Emerging Biotechnology Policy, NIH Office of Science Policy*

Sheri Hild, PhD, *Program Director for the National Primate Research Centers (NPRCs) at Office of Research Infrastructure Programs, NIH*

Ashley Parker, PhD, *Health Science Policy Analyst, NIH*

Yuao Zhu, PhD, *Pfizer*

FNIH STAFF

Stacey Adam, PhD, *Director, Cancer, Research Partnerships, FNIH*

Joseph P. Menetski, PhD, *Associate VP of Research Partnerships, FNIH*

Michael Santos, PhD, *Associate Vice President, Science, FNIH*

Rosa Maria Alvarez, PhD, *Senior Consultant*, *Monitor, Deloitte*

David Frankowski, PhD*, Writer, Rose Li and Associates, Inc*

Appendix B: Chat Transcript

From cat lutz to Everyone: 10:10 AM

sorry have to step away for a min

From Nancy Haigwood to Everyone: 10:13 AM

Agree completely with Kara

From Jay Rappaport to Everyone: 10:16 AM

We have the D614G strain and plan to test as soon as possible for comparison

From Josh Fessel (NIH/NHLBI) to Everyone: 10:28 AM

If I can be of help, I'm more than happy to do so re: combo therapies!

From Christine Colvis to Everyone: 10:36 AM

re:NHPs - This is another subgroup that I think could benefit from having a couple of people from the clinical WG participating.

From Jay Rappaport to Everyone: 10:48 AM

Glad to participate in that subgroup

From Jay Rappaport to Everyone: 10:57 AM

I think it will be important to identify changes in viral sequences in response to therapeutics and immune escape vaccines ....also changes in different compartments

I think AZT is a lesson here

From Kara Carter to Everyone: 10:58 AM

I am sorry, but I need to leave for another meeting.

High-Level Meeting Summary

The Therapeutics-Clinical (TX-Clinical) Working Group (WG) received updates from its Master Protocol and Agent Prioritization Subgroups (MPSG and APSG, respectively) and from the COVID-19 R&D Group about its parallel anti-COVID-19 efforts.

Master Protocol Subgroup Update

Dr. Stacey Adam presented on the status of the MPSG's various master protocols now under development:

- **ACTIV-1:** (phase III; immunomodulators; inpatients; Pre-IND submitted; August launch)
    - Sponsor: TBD + NCATS Trial Innovation Network (TIN) + CRO
- **ACTIV-2:** (seamless phase II/III; neutralizing monoclonal antibodies [mAbs]/antivirals; outpatients; IND submitted; July launch)
    - Sponsor: NIAID AIDS Clinical Trials Group (ACTG) + CRO
- **ACTIV-3:** (seamless phase II/III; neutralizing mAbs; inpatients; IND submitted; July launch)
    - Sponsor: NIAID INSIGHT + NHLBI PETAL + NHLBI CTSN + VA + CRO
    - ACTIV-3 will include phase I testing option for agents that need it
- **ACTIV-4:** (phase III; anticoagulants; pre-hospitalized/hospitalized/post-hospitalized; protocol in development; July launch)
    - Sponsor: NHLBI-NINDS Network of Networks

ACTIV-1: Immunomodulators (Inpatient Phase III)

Although the ACTIV-1 moniker will continue to circulate, the protocol has now received a distinct title: RAMP-C (RAndomized Master Protocol for Immune Modulators Treating COVID-19). The protocol's pre-IND was submitted to FDA on July 7 and FDA has notified ACTIV that its Division of Rheumatology and Transplant Medicine will respond within 10 to 14 days. The protocol team is simultaneously advancing on multiple fronts: it has identified Dr. William G. Powderly (from NCATS' TIN) as PI; has identified 45 network sites interested in participating (as of July 7); and is working with the Duke Clinical Research Institute (DCRI), which may become the trial sponsor and help oversee its DSMB oversight body. All other functions will be managed by a CRO that the protocol team will select from (b)(4) The NCATS/FNIH team is completing the scope of work to assist in (b)(4) (b)(4) and plans to release the document by July 15 and then to collect responses within one week.

ACTIV-2: Monoclonal Antibodies (Outpatient, Seamless Phase II/III)

The ACTIV-2 protocol team has finalized its response to FDA's pre-IND review and returned its New IND on July 6. With Version 1.0 of the protocol complete, ACTIV-2 can now advance on major aspects of trial execution. The team is currently collaborating with (b)(4) to launch its first study and will meet with (b)(4) this afternoon to begin drafting drug appendices for (b)(4) It continues to develop trial infrastructure in collaboration with the Division of AIDS (DAIDS) and PPD, a CRO. The logistics of ACTIV-2 will require considerable effort to recruit outpatient participants, who have been counseled for months to remain home but must now be encouraged to leave home for drug trials. ACTIV-2 is working with NIH to develop a public recruitment plan and is also assessing capacity to implement a home nursing plan to follow up with enrolled participants.

Discussion
Dr. Adam clarified that the main public relations efforts will include a single overarching announcement of all ACTIV protocols, given the proximity of their launch dates, in addition to protocol-specific efforts. The overarching public relations plan is being developed by communications staff in NIH's Office of the Director, NIAID, NHLBI, and ACTIV; once these staff members have developed a plan, they will share it with WG members and engage communications leads at participating companies.

ACTIV-3: Monoclonal Antibodies (Inpatient, Phase III (2 Stage))

The ACTIV-3 team had received comments on its pre-IND submission and is now resolving safety reporting suggestions in preparation to submit its New IND during the week of July 13. The protocol's extended 90-day follow-up requires refining several design details. Participating companies are working to develop Bayesian learning methods for the trial while operations planning for a July 29 launch continues with PETAL, CTSN, and VA teams, as well as a CRO.

ACTIV-4: Anticoagulants (Pre-hospitalized/Hospitalized/Post-hospitalized, Phase III)

The ACTIV-4 team is finalizing protocols for three patient populations. The hospitalized patient protocol is testing various doses of heparin and thus does not need an IND. The protocol has been finalized for Steering Committee approval and (if approved) will be submitted to DSMB members on July 13 for review at their July 17 meeting. Upon DSMB approval, the hospitalized patient trial can be implemented at two sites almost immediately. The pre-hospitalized patient protocol—which will test apixaban (2.5 and 5 mg twice daily), aspirin, and placebo—is being finalized. An IND is required to extend the label for apixaban, and the team is working with FDA to enable this extension. The ACTIV-4 team has also developed several approaches to managing outpatient logistics: it will ship drugs overnight to patients and will use a double consent approach, with the first consent secured during a blood draw at a COVID-19 testing site and the second conducted by phone. The post-hospitalized patient protocol is being developed and the team is attempting to synchronize it with other outpatient clinical trials, including ACTIV trials.

Agent Prioritization Subgroup Updates

Outpatient Treatments (under the ACTIV-2/3 protocol)

The Trial Oversight Committee (TOC) has endorsed the ACTIV-2/-3 Agent Selection Committee's (ASC) recommendation to approve (b) (4) for entry into ACTIV-2. The protocol team scheduled an initial planning meeting with Merck for July 9. The ASC is holding weekly mAb review meetings and most recently recommended that ACTIV quickly collect additional data for two potentially promising mAbs (from GSK-Vir and Brii Bio); the TOC agreed. The ASC will consider two additional mAbs this week as well as new data for previously reviewed agents.

Discussion

Dr. Timothy Buchman questioned the inclusion of an antiviral such as (b)(4) in (b)(4) (b)(4). Drs. (b)(6) and (b)(6) explained that the protocol (b)(4) (b)(4) Dr. Currier emphasized that this breadth is captured in the full name for ACTIV-2, which is ADAPT-OUT (for OUTpatient).

Antivirals

The Antivirals Subteam has collaborated with the Preclinical WG to complete a second round of prioritization for twelve new antivirals submitted after completion of Prioritization Wave 1. None of these agents had adequate data to support immediate ACTIV testing. One agent that appeared promising (b)(4) subsequently reported negative trial data (b)(4) The Subteam is currently collecting additional data on two agents: (b)(4). An additional four have been deferred and six have been eliminated from consideration.

Discussion

Dr. Keith Gottesdiener, who helped develop Montelukast, noted that it has not demonstrated any antiviral activity. Dr. Joan Butterton agreed that it has no *direct* antiviral activity but noted that Montelukast seems to indirectly inhibit viral entry via effects on pulmonary macrophages.

Immune Modulators

The Immune Modulators Subteam is collaborating with the Preclinical WG and several additional NIH reviewers to conduct a second wave of agent prioritization for eleven agents submitted through the ACTIV Compound Survey. The Subteam will assess whether to conduct direct outreach to companies to expand the candidate pool and, accordingly, whether to perform a staggered double review.

Symptomatic/Supportive Therapies

Dr. Adam informed the WG that only two symptomatic/supportive therapies have been submitted to ACTIV. Although this number is insufficient to require a formal prioritization meeting, reviewers who wish to proceed can contact Dr. Adam to discuss potential approaches.

COVID R&D Presentation

Dr. Gottesdiener delivered an update on parallel anti-COVID-19 efforts by the COVID R&D Group, an alliance of twenty top pharmaceutical firms established in March to accelerate treatments regardless of source. The R&D Group is dedicated to applying its unique capabilities strategically in order to complement rather than duplicate other COVID-19 efforts. Dr. Gottesdiener presented on its therapeutics work, which has pursued three primary approaches:

1. **Short-Term COMMUNITY Trials.** The R&D Group has developed a master protocol to test repurposed agents in hospitalized patients. Its first study, slated to launch in late July, will test three molecules (b)(4)) in

approximately (b) (4) per arm with continual sample size re-estimation. (b) (4) can enroll three additional agents in 2020 and more in 2021. The R&D Group has also encouraged developers to utilize ACTIV, I-SPY, REMAP, and other efforts.

2. **Long-Term Signal Trial Protocol.** The R&D Group is developing a phase Ib/IIa platform to test novel assets in sufficiently powered signal trials (100 to 150 patients) and thus accelerate promising agents into clinical trials. A similar effort exists in the U.K. but has been missing in the U.S. The R&D Group is finalizing a protocol sheet and is beginning prioritization of approximately 60 agents identified in collaboration with BioCentury. It will seek new sources of funding to ensure that promising agents from low-resource developers (including academic consortia and some biotech firms) are not overlooked.
3. **Future Infrastructure.** The R&D Group seeks to develop anti-COVID-19 infrastructure that can also lay the foundation for faster and more coordinated responses to the world's *next* pandemic. It has established a non-profit (Unify R&D) to lead this strategic effort in partnership with government and other private entities.

Discussion

Drs. Currier and Ruxandria Draghia-Akli inquired about the R&D Group's efforts to diversify trial sites. Dr. Gottesdiener reported that the group seeks whenever possible to identify networks that are not already participating in ACTIV trials, in order to avoid spreading resources too thinly and to expand overall capacity for pandemic response. The group is exploring sites that traditionally have not participated in such large-scale trial efforts as well as ex-U.S. sites (particularly in Southeast Asia). However, sites do need to have sufficient local infrastructure to support trials in the hospitalized patients prioritized by the R&D Group.

Dr. Adam asked whether the R&D Group is involved in efforts to develop a universal platform for master protocols of various types and to structure new highly versatile sites that could run trials under such a platform. Dr. Gottesdiener suggested that members of the group would be interested in such an effort but that it is not part of the group's current mandate.

ACTIV Brand

Participants discussed the development of distinct names for ACTIV protocols (including RAMP-C for ACTIV-1, ADAPT-OUT for ACTIV-2, and TICO [Therapeutics for In-Patient Treatment of COVID-19] for ACTIV-3) and their potential to undermine the coherence of the effort's public profile. Mr. David Wholley explained that various rules govern the assignment of protocol names. He and Dr. Adam reported that communications staff also observed that ACTIV's use of a numbering system may create confusion, in part because its numbers do not correspond to the order in which the protocols will launch. He noted that Dr. Francis Collins desires a naming convention that balances common ACTIV nomenclature, the desire for clarity, and the need to follow naming conventions. NIH communications staff are working on this effort.

Next Steps

The WG's next meeting will feature a presentation by Dr. Michael Santos on behalf of the Vaccines WG.

Appendix A: Participants List

WORKING GROUP MEMBERS

Neil Aggarwal, MD, *Lung Biology and Disease Branch Chief, NHLBI*

Sam Bozzette, MD, PhD, *Chief Medical Officer, National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH)*

Timothy G. Buchman, MD, PhD, *Biomedical Advanced Research and Development Authority (BARDA)*

Joan Butterton, MD, *Associate VP, Clinical Research, Infectious Diseases, Merck & Co.*

Judith Currier, MD, *Professor of Medicine in the Division of Infectious Diseases, University of California, Los Angeles (UCLA)*

Angelo DeClaro, MD, *Division Director (Acting), Division of Hematologic Malignancies, Food and Drug Administration (FDA)*

Ruxandra Draghia-Akli, MD, PhD, *Global Head, Global Public Head R&D, Johnson & Johnson*

Keith Gottesdiener, MD, *Former President and Chief Executive Officer, Rhythm*

Elizabeth (Libby) Higgs, MD, MIA, DTM&H, *Global Health Science Advisor, National Institute of Allergy and Infectious Diseases (NIAID)*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis (WG Co-chair)*

Andrei Kindzelski, MD, PhD, *Program Director, Division of Blood Diseases and Resources, National Heart, Lung, and Blood Institute (NHLBI)*

Lisa LaVange, PhD, *Associate Chair, Department of Biostatistics, UNC*

John Mellors, MD, *Professor of Medicine, Chief of Infectious Diseases Division, U. Pittsburgh*

Naimish Patel, MD, *Global Development Head of Therapeutic Area, Immunology and Inflammation, Sanofi*

Dionne Price, PhD, *Director, Division of Biometrics IV, CDER, FDA*

Michael Proschan, PhD, *Mathematical Statistician, Biostatistics Research Branch, NIAID, NIH*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH (WG Co-chair)*

Lora Reineck, MD, *Program Director, Lung Biology and Disease Branch, NHLBI*

Daniel Rubin, PhD, *Division of Biometrics IV, CDER, FDA*

INVITED PARTICIPANTS

Christine Colvis, PhD, *Director for Drug Development Partnership Programs, NCATS, NIH*

Michelle Culp, MPH, *Office of the Director, NIH*

Joshua Dettman, PhD, *Assistant Group Leader, MIT Lincoln Laboratory*

Ellen Gadbois, PhD, *Office of Science Policy, Office of the Director, NIH*

STAFF

Stacey Adam, PhD, *Director, Cancer, Foundation for the NIH (FNIH)*

Karen Tountas, PhD, *Scientific Program Manager, FNIH*

David Wholley, MPhil, *Senior VP of Research Partnerships, FNIH*

Helen Q. Chen, PhD, *Senior Consultant, Deloitte*
Benjamin Stratton, *Senior Consultant, Deloitte*

Dana Carluccio, PhD, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

From (b)(6) to Everyone: 01:26 PM

Will the (b)(4) trial be reaching out to sites separate from the soon-to-be-launched ACTIV (1-4) trials?

From Keith Gottesdiener to Everyone: 01:37 PM

Yes. I think I tried to answer this verbally but if any add'l questions, please let me know.

From Timothy Buchman to Everyone: 01:37 PM

You did, thanks...

From John Mellors to Everyone: 01:54 PM

https://www.who.int/news-room/detail/04-07-2020-who-discontinues-hydroxychloroquine-and-lopinavir-ritonavir-treatment-arms-for-covid-19

From (b)(6) to Everyone: 01:55 PM

Their last paragraph:
This decision applies only to the conduct of the (b)(4) trial in hospitalized patients and does not affect the possible evaluation in other studies of (b)(4) in non-hospitalized patients or as pre- or post-exposure prophylaxis for COVID-19. The interim (b)(4) results are now being readied for peer-reviewed publication.

From (b)(6) to Everyone: 01:56 PM

Also NEJM study early on in severe COVID was (b)(5)

High-Level Meeting Summary

The Vaccines Working Group (WG) convened to discuss two brief updates – regarding the Vaccine-Associated Immune Enhancement Sub-Group's manuscript and the Vaccines Clinical Trials Sub-Group's article on the operational considerations of human challenge studies – and COVID-19 disease disparities and clinical trial populations. Participants agreed that representation of under-represented communities of color is imperative within clinical trial populations.

Vaccine-Associated Immune Enhancement Sub-Group Updates

The Vaccine-Associated Immune Enhancement Sub-Group is incorporating feedback from the Vaccines WG into the Sub-Group's manuscript. Drs. Ann Arvin and Bart Haynes will edit the updated manuscript and share it with the Vaccine WG for review. Once the manuscript has been finalized and approved by the Vaccine WG, the manuscript will be submitted to a journal for publication and Dr. Paul Offit will use the manuscript to develop a one- to two-page lay synopsis version (possibly in Q&A format) to share with a broader audience.

Clinical Trials Sub-Group Updates

The Clinical Trials Sub-Group's article on the operational and bioethical considerations of controlled human infection models (CHIMs) will be published today in the *New England Journal of Medicine.* The article concludes that CHIM models for SARS-CoV-2 and other HCoVs may have complementary value to traditional clinical trials, but CHIM models requires at least one year to develop and thus are not expected to accelerate the initial evaluation of vaccine safety and efficacy. The article recommends developing CHIMs for concurrently with ongoing efficacy trials for potential future use.

Dr. Doug Lowy noted that Dr. Cristina Cassetti (NIAID) organized a meeting of representatives from NIAID, NCI, and the NIH ethics to discuss what is recommended in the article: to begin development of CHIMs in parallel.

Dr. Jerry Sadoff noted Janssen has been thinking about human challenge studies as well. If a successful vaccine reduces capacity to run traditional efficacy trials for other candidates, a CHIM could facilitate comparison of vaccines.

COVID-19 Disease Disparities and Clinical Trial Representation

Black and Latinx populations are disproportionately impacted by COVID-19, compared to White populations; these populations experience higher rates of disease, hospitalization, and death due to COVID-19. In particular, 4x to 10x increased risks of death for Black and Latinx populations over the ages of 35-74 compared to White populations. Black and Latinx populations have higher rates of diagnosis with COVID-19, but their age-adjusted rates of hospitalization and death are even higher than that, suggesting (with caveats related to data quality) that the outcomes per case are worse for Black and Latinx patients than for White patients. The data shown were for US populations, but analyses of UK populations [see appendix slide] show similar trends.

The vaccine development effort needs to be inclusive, which means multi-generational and multi-racial diversity representative of the US. It is important for publicly-funded clinical trials to enroll a patient population representative of the general US population.

Dr. Lowy posed the following questions to facilitate discussion:

- What population representations are important for primary analysis and final analysis?
- Is a trade-off in recruitment speed justified to increase representation?
- How can the Vaccines WG help accelerate recruitment of populations?

Discussion

Participants agreed on the importance of enrolling representative populations in clinical trials. In order to enroll significant numbers of these populations, the research community must address their general distrust of these populations in the federal government and government-associated researchers. This distrust stems from multiple past studies that treated African American and Hispanic individuals as test subjects (e.g., the Tuskegee study) instead of the population who would receive the benefits of the clinical trial, and has been heightened within the general population through recent events (e.g., Black Lives Matter movement).

The COVID-19 Prevention Network (CoVPN) has a significant program for community engagement, at the national and site level, where sites have long histories of engaging with their communities. One of the questions is how to extend this capacity across the CRO sites that will be participating in the trials. Dr. Nelson Michael recognized the work of the CoVPN and their collaboration with other agencies and organizations to lend their expertise in this area, including addressing the counter-narratives about clinical trials as experiments on people of color. Dr. Kelly Gebo of All of Us also cited the presence of the counter-narrative in their community outreach, and described positive engagement with the CoVPN community engagement team and their approach to addressing this challenge. One of the questions in focus groups is whether vaccines will be available to communities of color when vaccine become available, and whether the government can provide assurances of this.

To engage with these sub-populations, Dr. Arvin suggested engaging with healthcare providers within nursing homes, who are essential workers and disproportionately people of color. Dr. Hotez noted the high percentages of Black and Latinx patients in ICUs in Texas metro areas and along the Mexican border, and suggested identifying trial sites there and that can reach Native American populations. Dr. Larry Corey noted that the ACTIV clinical trial network includes sites within Oklahoma and the Southwest United States, with access to Native American populations.

Dr. Macaya Douoguih stated J&J's commitment to focus on higher-risk populations, including Black, Latinx, and older participants, and expressed a desire to align and collaborate on approaches to reaching these populations. Dr. Jackie Miller said that Moderna's teams have been in close contact with CoVPN, and Moderna is asking non-CoVPN sites to put together diversity plans. Dr. Tonya Villafana said that this is also an active an ongoing discussion within the AstraZeneca team. Dr. Greg Glenn agreed that Novavax thinks this information is extremely important for the trials and agrees that this is both ethically and practically important; Dr. Glenn also inquired whether causes of these disparities could be better understood.

Dr. (b)(6) [redacted] asked if the group (b)(5) [redacted]. Dr. (b)(6) [redacted] said (b)(5) [redacted] Dr. (b)(6) [redacted] suggested the (b)(5) [redacted] Dr. (b)(6) [redacted] noted (b)(5) [redacted].

Participants discussed how (b)(5) [redacted]

Dr. Gebo noted that the All of Us Study research team and participants are interested in engaging with these trials, and also pointed out that there are other research programs that have engaged under-represented populations that may also be valuable to connect with.

Dr. Corey stated the important of raising awareness of these issues and the potential tensions involved. Dr. Corey invited participants to share additional perspectives on approaches to achieving representation in the trials with him, Dr. Lowy, or Dr. Santos via email. Dr. Lowy recommended discussing in a future meeting on what is feasible to do given that trials are starting soon and how the Vaccines WG can best support that.

Appendix A: Participants List

WORKING GROUP MEMBERS

Douglas Lowy, MD, *Principal Deputy Director, National Cancer Institute (NCI)*

Ann Arvin, MD, *Professor of Pediatrics and Microbiology & Immunology, Stanford University*

Larry Corey, MD, *Professor and Principal Investigator, University of Washington and HIV Vaccine Trials Network, and Past President and Director, Fred Hutchinson Cancer Research Center*

Susan Buchbinder, MD, *Director of Bridge HIV, San Francisco Department of Public Health, and Professor, UCSF*

Gregory Glenn, MD, *President, Research and Development, Novavax*

Barton Haynes, MD, *Director, Human Vaccine Institute, Duke University School of Medicine*

Peter Hotez, MD, PhD, *Dean for the National School of Tropical Medicine, Baylor College of Medicine, and Director, Texas Children's Center for Vaccine Development*

Antonio Lanzavecchia, MD, *Director, Immune Regulation, Institute for Research in Biomedicine*

Peter Marks, MD, PhD, *Director, Center for Biologics Evaluation and Research (CBER), U.S. Food and Drug Administration (FDA)*

Nelson Michael, MD, PhD, *Director, Center for Infectious Disease Research, Walter Reed Army Institute of Research*

Paul Offit, MD, *Professor, University of Pennsylvania, and Director, Vaccine Education Center, Children's Hospital of Philadelphia*

Michael Santos, PhD, *Associate Vice President, Science, FNIH*

Hanneke Schuitemaker, PhD, *Global Head, Viral Vaccine Discovery and Translational Medicine, Janssen Pharmaceutical Companies of Johnson & Johnson*

Brett Tolman, MA, *Strategy Manager, Deloitte*

Tonya Villafana, PhD, MPH, *Global Medicines Leader, Infectious Diseases, AstraZeneca*

INVITED PARTICIPANTS

Alison Albert, MPH, *Associate Director for Communications and Outreach, Division of Bacterial Diseases, National Center for Immunization and Respiratory Diseases, CDC*

Kathleen Callahan, MS, *Vice President, Regulatory Affairs, Chemistry, Manufacturing, and Controls, Novavax*

Michelle Culp, BSN, MPH, *Senior Advisor, Office of Science Policy, NIH*

Macaya Douoguih, MD, MPH, *Head, Clinical Development and Medical Affairs, Janssen*

Filip Dubovsky, MD, MPH, *Senior Vice President and Chief Medical Officer, Novavax*

Emily Erbelding, MD, MPH, *Director, Division of Microbiology and Infectious Diseases, NIAID, NIH*

Ellen Gadbois, PhD, *Program Lead, Biosafety, Biosecurity, and Emerging Biotechnology Policy Division, Office of Science Policy, NIH*

Kelly Gebo, MD, MPH, *Chief Medical and Scientific Officer, All of Us Research Program, NIH*

Paul Gillard, MD, *Senior Director, Clinical Development, GlaxoSmithKline (GSK)*

Peter Gilbert, PhD, *Biostatistician, Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center*
Holli Hamilton, MD, MPH, *Senior Medical Officer, BARDA*
Ian Hirsch, PhD, *Statistics Team Leader, AstraZeneca*
Kenneth Koury, PhD, *Biostatistician, Pfizer*
Jackie Miller, MD, *Senior Vice President, Infectious Disease Development, Infectious Diseases, Moderna*
Ashley Parker, PhD, *Health Science Policy Analyst, NIH*
Jerry Sadoff, MD, *Head of Early Development, Crucell Vaccine Institute, Janssen Pharmaceutical Companies of Johnson & Johnson*
Vivek Schinde, MD, MPH, *Vice President, Vaccine Clinical Development, Novavax*
Natalie Thornburg, PhD, *Lead Microbiologist, Respiratory Viruses Branch, CDC*
Jennifer Verani, MD, MPH, *Epidemic Intelligence Service Officer, Division of Global Health Protection, Center for Global Health, CDC*

FNIH STAFF
Stacey Adam, PhD, *Science Program Manager, Foundation for the NIH (FNIH)*
Stephanie James, PhD, *Senior VP of Science, FNIH*

Bethany Stokes, MS, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

from Kelly Gebo to everyone:

Kelly Gebo from All of Us study here. Last night we had a great conversation about ways to include our diverse participants with the CO VPN engagement team. We are keen to share best practices with recruiting and retaining traditionally understudied populations. We have already learned a lot from conversations with our participant boards on a potential All of Us- ACTIV relationship.

High-Level Meeting Summary

The Preclinical Working Group (WG) discussed how new strains of SARS-CoV-2 may alter current COVID-19 preclinical models and the timeline to transition from design to maintenance phases.

Action Items

- Sub Groups to review timeline for July deliverables and define which items are necessary to complete by July and which ones would be ‘nice to have’
- Dr. Jim Anderson will discuss with NIAID the possibility of leveraging NHP resources from OAR in the short term.

Selection of a SARS-CoV-2 Reference Strain

Dr. (b)(6) has contacted (b)(4) about the cost and time involved in scaling viral stock and is awaiting their reply. During discussions with the vendor, (b)(4) Additional experiments are underway to generate the most appropriate protocol for generating high quality virus stock. After these experiments have concluded, the SOP can be set, the release characteristics defined and alternative vendors can be approached.

Dr. (b)(6) has suggested considering SARS-CoV-2 strain containing the D614G mutation as a reference strain, because this appears to be most prevalent strain and could be the most infectious. (b)(6) is in contact with (b)(4) and getting more information on (b)(4) SARS-CoV-2 strain with the D614G mutation instead of the (b)(4) as its primary reference strain (or to use both strains in parallel).

Dr. (b)(6) has created (b)(4) with and without the D614G mutation. Although analyses of virus stability and infectivity are ongoing, preliminary results show general similarity between D614G (b)(4). (b)(4) However, the peak titer is the same for both.

To support robust safety testing of vaccines, it is crucial that the most pathogenic and common strain in circulation is selected as the reference strain. Participants also noted that strain differences will be particularly important in virus enhancement studies and will be critical for understanding COVID-19 pathogenesis and infectivity.

WG Transition from Design to Maintenance Phases

The Preclinical WG is transitioning from designing COVID-19 research support infrastructures to implementing and maintaining them. Dr. Joseph Menetski provided a list of tasks being conducted by each subgroup and asked each subgroup to discuss which items *must* and which would *ideally* be finished by July 31, and which could be moved into a future maintenance phase.

NCATS OpenData Portal

The OpenData Portal Subgroup has already published animal model summaries and will produce corresponding detailed model summaries by July 7 (for release on the Portal by July 12). Proposed processes to maintain Portal data will be drafted by July 16. Dr. Jay Rappaport and Ms. Samantha Jonson will also design an outline of the study-level data for the Tulane NPRC data repository by July 31. Ideally, the Subgroup would incorporate additional in vitro assays into the Portal, add the Pandemic Response SOP manuscript to its resources tab, and release a document on best practices for using animal models when developing and testing COVID-19 treatments. Publication of BSL 3/4 best practices may not be completed until further into the future.

In Vivo Strategy and NHP Study Prioritization

The *In Vivo* Strategy Subgroup will ensure that NHP master protocols are finalized for review by July 31. It hopes to also provide a guidance document for conducting studies involving mouse and other small animal models by July 31.

Dr. Jim Anderson requested that the WG contribute to, and perhaps lead, an NHP prioritization advisory panel composed of members from several organizations (e.g., Preclinical WG, (b)(4) NIAID, NPRCs, and OWS). This panel would aim to conserve NPRC resources by coordinating, prioritizing, and approving studies that will receive NHPs. It could potentially also coordinate transportation of NHPs among facilities within the U.S. and import NHPs from outside the U.S. (e.g., African Green monkeys from St. Kitts). Dr. Anderson noted that NIH may be able to grant NPRCs access to NHPs from the Office of AIDS Research (OAR), as long as they are replaced.

BSL Network/ACTIV Resource Coordination Group

The BSL Network Subgroup has been tasked with finalizing a list of BSL 3/4 sites, determining any additional BSL capabilities information, and identifying the needs and funding requirements of these facilities, thus enabling a Resource Coordination Group to connect researchers to BSL 3/4 sites with shared interests that can together develop COVID-19 treatments. The Subgroup did not have time to discuss the timeline of these activities and will contact Dr. Menetski with suggestions. However, a key next step is to develop a survey to gather interest in joining ACTIV as well as collecting study preferences and capabilities for each site

Next Steps

All subgroup members will review the slides during their Sub Group meetings to prioritize and provide deadlines for each task. Dr. Young will discuss with the ACTIV EC which SARS-CoV-2 strain should be selected as ACTIV's primary viral reference strain. Dr. Anderson will discuss with NIAID the possibility of leveraging NHP resources from OAR in the short term.

Appendix A: Participants List

WORKING GROUP MEMBERS

Peter Adams, PhD, (not in attendance) *Health Scientist, Project Officer, BARDA*

Annaliesa Anderson, PhD, (not in attendance) *Vice President and CSO Bacterial Vaccines, Pfizer*

Ralph Baric Professor, PhD, *Dept. of Epidemiology and Dept. of Micobiology and Immunology, UNC Chapel Hill*

Kara Carter, PhD, *Senior Vice President Infectious Disease, Evotec*

Marc Charette, PhD, *Division of Cardiovascular Diseases NIH, NHLBI*

Tomas Cihlar, PhD, *VP, and Head of Virology, Gilead*

Christine Colvis, PhD, *Director, Drug Development Partnership Programs, NCATS*

Damon Deming, PhD, (not in attendance) *Virologist, Division of Antiviral Products, Office of New Drugs, FDA*

Michael Diamond, MD, PhD, (not in attendance) *Professor, Depts. of Medicine, Molecular Microbiology, Pathology & Immunology, Washington University*

Ken Duncan, PhD, *Gates Foundation*

Prabhavathi Fernandes, PhD, *Retired, most recently led biotechs Cempra and DarPharma*

Josh Fessel, MD, PhD, *Division of Lung Diseases NIH, NHLBI*

Clint Florence, PhD, *Program Officer, Research Resource Section, OBRR, DMID, NIAID*

Greg Gatto, PhD, (not in attendance) *Drug Development Regulatory Project Leader, RTI*

Jay Grobler, PhD, *Director, Infectious Disease Biology, Merck*

Nancy Haigwood, PhD, *Director and Professor, Oregon National Primate Research Center, OHSU*

Judith Hewitt, PhD, *Deputy Director, Office of Biodefense, Research Resources and Translational Research, NIAID*

Samantha Jonson, MPS, *Special Assistant to the Director, NCATS*

Cat Lutz, PhD, *Senior Director, Mouse Repository & In Vivo Pharmacology, Rare and Orphan Disease Center, Jackson Laboratory*

Frank Nestle, MD, (not in attendance) *Global Head of Immunology Therapeutic Research Area and Chief Scientific Officer North America, Sanofi*

Liz Ottinger, PhD, *Project Manager, NCATS*

David Payne, PhD, DSc, (not in attendance) *Vice President & Head, Medicine Opportunities Research Unit, GSK*

Louise Pitt, PhD, *Director, Center for Aerobiological Sciences, USAMRIID*

Tony Punturieri, MD, PhD, *Division of Lung Diseases NIH, NHLBI*

Srinivas Rao, MBA, PhD, *Global Head Translational In Vivo Models, Sanofi*

Jay Rappaport, PhD, *Director and Chief Academic Officer, Tulane Primate Center*

John Young, PhD, *Global Head Infectious Diseases and Vice President, Roche*

INVITED PARTICIPANTS

James M. Anderson, M.D., Ph.D., Deputy Director for Program Coordination, Planning, and Strategic Initiatives, NIH

Ellen Gadbois, *Program Lead, Emerging Biotechnology Policy, NIH Office of Science Policy*

Sheri Hild, PhD, *Program Director for the National Primate Research Centers (NPRCs) at Office of Research Infrastructure Programs, NIH*

Felicia Qashu, PhD, *Program Officer at National Institutes of Health*

FNIH STAFF

Stacey Adam, PhD, *Director, Cancer, Research Partnerships, FNIH*

Joseph P. Menetski, PhD, *Associate VP of Research Partnerships, FNIH*

Rosa Maria Alvarez, PhD, *Senior Consultant*, *Monitor, Deloitte*

Benjamin Stratton, PhD, *Senior Consultant, Deloitte*

David Frankowski, PhD*, Writer, Rose Li and Associates, Inc*

Appendix B: Chat Transcript

From Liz Ottinger to Everyone: 10:02 AM

I don't know if others have already seen this database on repurposing from Dr. David Fajgenbaum at UPenn. There was an article in CNN a couple of days ago on it also.

https://cdcn.org/corona/

https://www.cnn.com/2020/06/27/health/coronavirus-treatment-fajgenbaum-drug-review-scn-wellness/index.html

From Josh Fessel (NIH/NHLBI) to Everyone: 10:04 AM

Thanks Liz! The CORONA registry/database is really interesting, and the story behind it equally so.

From Christine Colvis to Everyone: 10:58 AM

And the clinical group

Action Items

- Dr. Tountas will add discussion of the long-term use of dashboard data to the agenda for the next meeting.
- Dr. Tountas and the WG Co-Chairs will form two- to three-person teams of WG member volunteers to create four additional playbooks.
- Dr. Kublin will provide Dr. Kurilla with a point of contact in the HHS CIO office.

High-Level Meeting Summary

The Clinical Trial Capacity Working Group (CTC WG), co-chaired by Elizabeth Desrosiers and Michael Kurilla, convened to receive a debrief of the Executive Committee meeting on June 17, prioritize playbook development, and review dashboard updates.

The Executive Committee approved the WG Co-Chairs definition of "ACTIV involvement," which clarifies who may be granted access to the geotracking dashboard.

The WG will form small teams of WG member volunteers to create playbooks for e-consent, site training and tools, remote monitoring, and electronic Clinical Outcome Assessment (eCOA)/"bring-your-own-device" (BYOD)/hybrids. The Innovations Sub-Group will discuss whether another highly rated topic—recruitment—would be best addressed as a playbook topic or as part of the Innovations Toolkit.

The WG continues to refine the geotracking dashboard and to explore other forecasting tools.

Below is a summary of the key discussion themes.

Executive Committee Meeting Debrief

During the Executive Committee meeting on June 17, the WG Co-Chairs reviewed the WG's progress on the geotracking dashboard, surveys, innovations, and the Recommendations subcommittees. Dr. Francis Collins confirmed that NIH is committed to maintaining the Clinical Trial Capacity's inventory of clinical networks, sites, and innovations.. The EC acknowledged that the composition, experience, and capacity of the networks and sites will change over time; discussions about how inventory maintenance will be operationalized are ongoing.

The Co-Chairs proposed a definition of "ACTIV involvement" to clarify who may be granted access to the survey data—and thus the dashboard. The EC approved the CTC WG to designate individuals as involved in ACTIV if they are (1) staff working on COVID-related efforts at companies that are ACTIV Leadership members with the intent of public health benefit and/or to eliminate duplication of efforts; (2) individuals working on the development and/or execution of ACTIV-branded clinical trials; or (3) staff involved in COVID-related efforts at organizations coordinating and/or aligning with ACTIV for public health benefit and/or to eliminate duplication of efforts. The intent is to make the data as broadly available as possible, while honoring the parameters to data sharing approved by the survey respondents.

WG Discussion

WG members agreed that ACTIV should regularly and strategically communicate its activities and progress to the external research community in order to best leverage networks and relationships that have been cultivated over many years. This will be communicated to ACTIV leaders.

Playbook Prioritization

The Deloitte Team has migrated the Home Nursing Playbook created by Merck and Novartis from Excel to Word to improve the playbook's navigation and visual appeal.

This WG and the Therapeutics-Clinical WG have prioritized creation of playbooks for e-consent, site training and tools, remote monitoring, and eCOA/BYOD hybrids. During its meeting on June 25, the Innovations Sub-Group will discuss whether another highly rated topic—recruitment—would be best addressed as a playbook topic or as part of the Innovations Toolkit.

Dr. Tountas and the WG Co-Chairs will form two- to three-person teams of WG member volunteers to create the playbooks. WG members may nominate subject matter experts from their organizations to serve in their stead.

Dashboard Update

Mr. Wachtel described recent updates to the dashboard.

- Sites that did not complete the survey but are listed on a network roster are delineated by an "x" on the map.
- Networks and sites that will participate in ACTIV-branded trials will be clearly labeled as such.
- All survey responses can be easily exported to Excel.
- A user guide and resource tab is under development.

The WG continues to explore forecasting tools. Dr. Kublin will provide Dr. Kurilla with a point of contact in the HHS Office of the Chief Information Officer, which conducts most of its forecasting using the HHS Protect database. In addition, the WG will research Columbia University's Shaman Group model.

Dr. Goff inquired about the ability to incorporate a network-of-networks feature, which he and Mr. Wachtel will discuss in more detail.

Appendix A: Participants List

WORKING GROUP MEMBERS

Lionel Bascles, PhD, *Senior VP, Global Head of Clinical Sciences & Operations, Sanofi*

Myron Cohen, MD, *Associate Vice Chancellor for Global Health and Medical Affairs, Director, Institute for Global Health & Infectious Diseases, University of North Carolina Chapel Hill*

Larry Corey, MD, *Professor and Principal Investigator, University of Washington and HIV Vaccine*

Victoria Davey, PhD, MPH, *U.S. Department of Veterans Affairs*

Elizabeth Desrosiers (Co-Chair), MS, PMP, *Executive Director, Clinical Sciences and Study Management, Merck*

James Dickens, *Program Manager, National Center for Advancing Translational Sciences*

David Goff, MD, PhD, *Director, Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute (NHLBI)*

Michael Kurilla (Co-Chair), MD, PhD, *Director – Division of Clinical Innovation, National Center for Advancing Translational Sciences (NCATS)*

George Mensah, MD, *Director, Center for Translation Research & Implementation Science, National Heart, Lung, and Blood Institute (NHLBI)*

Seema Nayak, MD, *Director, Office of Clinical Research Resources, National Institute of Allergy and Infectious Diseases (NIAID)*

Manizhe Payton, *Director, Office of Clinical Site Oversight, National Institute of Allergy and Infectious Diseases*

Michael Vincent, MD, PhD, *Senior Vice President, Chief Scientific Officer of Inflammation and Immunology Research and Development, Pfizer*

INVITED PARTICIPANTS

Michelle Culp, *Office of Science Policy, NIH*

Penny Heaton, MD, *Chief Executive Officer, Bill & Melinda Gates Medical Research Institute*

Eric Hughes, MD, PHD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis*

James Kublin, MD, MPH, *Fred Hutchinson Cancer Research Center, and University of Washington*

FNIH STAFF

Stacey Adam, PhD, *Director, Cancer*

Stephanie James, PhD, *Senior VP of Science*

Karen H. Tountas, PhD, *Scientific Program Manager, Science*

Jonathan Wachtel, *Manager, Deloitte*

Nancy Tuvesson, MBA, *Writer, Rose Li and Associates, Inc.*

High-Level Meeting Summary

The Therapeutics-Clinical (TX-Clinical) Working Group (WG) heard updates from its Master Protocol Subgroup (MPSG) and Agent Prioritization Subgroup (APSG) and discussed how to establish Community Advisory Boards to help oversee ACTIV trials.

Master Protocol Subgroup Update

The MPSG presented on the status of its various master protocols now under development:

- ACTIV-1 (phase III; immunomodulators; inpatients; projected July launch)
- ACTIV-2 (phase II/III; neutralizing mAbs; outpatients; projected July launch)
    - ACTIV-2 will also include testing of antiviral agents
- ACTIV-3 (phase II/III; neutralizing mAbs; inpatients; projected July launch)
    - ACTIV-3 will include phase I testing option for agents that need it
- ACTIV-4 (phase III; anticoagulants; inpatients; projected July launch)

ACTIV-1: Immunomodulators (Inpatient Phase III)

The ACTIV-1 writing team continues to examine the RECOVERY study results and discuss their implications for the ACTIV-1 study design. Based on that examination, they have decided to incorporate a blinded, interim sample size re-calculation analysis). NIAID's Division of Allergy, Immunology, and Transplantation (DAIT) has decided not to sponsor ACTIV-1. Therefore, the ACTIV-1 team continues to liaise with CROs interested in potentially sponsoring ACTIV-1. The team also continues to collaborate with the NCATS Trial Innovation Network (TIN), which will oversee operational planning and trial implementation. TIN released its "Expression of Interest" survey to its sites and conducted a webinar to recruit sites—open questions from that webinar will be shared with the TX-Clinical WG for consideration.

The ACTIV-1 operations team has identified six potential CROs to provide operational support for trial implementation and is currently conducting due diligence to narrow its choices. As part of that process, the team will explore each CRO's capabilities to hold the IND and sponsor the trial. Next steps are to finalize a sponsor, network, and supporting CRO for ACTIV-1; contact FDA about submitting a Pre-IND ahead of sponsor identification; and submit the protocol for Pre-IND review. Dr. Peter Stein confirmed that submitting a Pre-IND for review—even before identification of a trial sponsor—would help to expedite the subsequent IND review. He also confirmed that all three agents to be tested under ACTIV-1 can be covered by a single master IND if that IND is linked to the original INDs for each pre-approved compound.

Discussion

Whereas the ACTIV Executive Committee previously expressed (b)(5) [redacted] (b)(4) [redacted] for ACTIV-1 testing, (b)(5) [redacted] (b)(4) [redacted]:. Specifically, (b)(5) [redacted]

Participants confirmed that ACTT-2 will complete enrollment within the next 2 weeks, and data from ACTT-2 may also help inform adaptations to ACTIV-1 and other ACTIV protocols.

ACTIV-2: Monoclonal Antibodies (Outpatient, Phase II/III)

The ACTIV-2 writing team has been working to address comments from FDA on its Pre-IND submission and expects to finalize Version 1.0 of the master protocol by July 1 for its official IND submission. In collaboration with company representatives, the ACTIV-2 team is delineating the trial's timing, process, and governance, as well as the legal implications for disclosure of interim data to the participating companies. The team expects to complete all necessary operational preparations and to initiate the trial by late July. NIAID's Division of AIDS (DAIDS) continues to work closely with PPD (a CRO) to coordinate execution of trial implementation; PPD is facilitating Operations meetings. Finally, the ACTIV-2 operations team continues to design and deploy a public relations campaign to help ensure adequate trial recruitment of outpatients (especially in underserved populations). Next steps are to use FDA comments to finalize protocol updates and submit a New IND and to continue planning for protocol implementation.

Discussion

Dr. (b)(6) [redacted] explained (b)(5) [redacted] (b)(4) [redacted] (b)(5) [redacted] Dr. (b)(6) [redacted] (b)(5) [redacted] Dr. (b)(6) [redacted] asked (b)(5) [redacted]

ACTIV-3: Monoclonal Antibodies (Inpatient, Phase II/III)

The ACTIV-3 master protocol was submitted to FDA for Pre-IND review on June 17, 2020. The ACTIV-3 team is awaiting FDA's comments and will work on drafting its response and updating the master protocol in preparation for subsequent IND submission. The team is also working closely with representatives from (b)(4) [redacted] to develop the agent-specific appendix (Appendix H1) for (b)(4) [redacted] agent. Operational planning for activation of ACTIV-3 also continues to progress; the INSIGHT team continues to work with PETAL, CTSN, and VA, as well as with the selected CRO to coordinate on execution of trial implementation. The ACTIV-3 team has received commitments from (b)(4) [redacted] to provide (b)(4) [redacted] supply for the trial and an official agreement to that effect is now being drafted. The team expects to launch the trial by the end of July, with additional agents entering the trial during August.

ACTIV-4: Anticoagulants (Inpatient, Phase III)

ACTIV-4 will initially include three studies: (1) in-hospital low-dose prophylaxis versus high-dose treatment; (2) pre-hospital antithrombotic prophylaxis; and (3) post-discharge antithrombotic prophylaxis. The first trial has been slightly delayed but is expected to launch by mid-July.

Agent Prioritization Subgroup Updates

The APSG continues to collect preclinical and clinical data on candidate agents through the ACTIV Compound Survey. As of June 25, the team has received 35 completed submissions.

Jointly with the Preclinical WG and Operation Warp Speed (OWS), the APSG's Antiviral Subteam has begun Wave 2 Prioritization of antivirals. The Subteam decided to focus exclusively on antivirals submitted through the Compound Survey for its first round of evaluation to ensure that all data are consistent, complete, and comparable (11 agents total). The APSG plans to actively request that companies interested in being considered for ACTIV testing submit their full data packages through ACTIV's Compound Survey. Dr. Rosa Maria Alvarez will email members of the TX-Clinical WG to collect information on company contacts that may be leveraged to solicit more data submissions. Scoring and selection of the current set of antiviral candidates should be completed by July 1 and the Subteam anticipates completing scoring and selection of the next round of antivirals by July 16.

The Neutralizing Antibody Agent Selection Committee, consisting of NIH and OWS members as well as academic experts, is now established and plans to review and adjudicate two to three agents per week, prioritizing review of agents that are ready to enter the clinic; eight companies have so far expressed interest in providing agents for testing. The Agent Selection Committee will submit its recommendations to the Trial Oversight Committee, which must then review and endorse them before any agent can enter ACTIV-2 and/or ACTIV-3 master protocols.

Next steps for the APSG are to continue Wave 2 Agent Prioritization for antivirals, continue to collect preclinical and clinical data on investigational agents via the ACTIV Compound Survey for the prioritization and selection committees to evaluate, and assemble prioritization subteams for host-targeted therapies/immunomodulators and for symptomatic/supportive compounds.

Discussion
Dr. Jacqueline Kirchner asked what minimum toxicology requirements had been established for agents entering ACTIV-2. Dr. Stacey Adam noted that ACTIV-2 will maintain higher toxicology standards than ACTIV-3, because as an outpatient trial ACTIV-2 will not be able to monitor patient safety as closely as ACTIV-3. Dr. Adam will send the official requirements to Dr. Kirchner (copying Dr. Garner so that he can forward it to representatives from Amgen).

Dr. Adam also noted that if prioritized agents do not fit well into any of the four ACTIV protocol designs above, the group may revisit the possibility of establishing its 'De Novo' ACTIV-5 master protocol. However, the priority will be to attempt to leverage the four existing protocol designs to test any agents of interest.

Community Advisory Board(s)

Participants briefly discussed the need to establish community advisory boards (CABs) for ACTIV trials and suggested leveraging and connecting the existing ACTG and INSIGHT CABs; these CABs are enthusiastic and well-versed in clinical trials and could be further supplemented with added representatives of patient communities. Further discussions are needed to determine how to organize ACTIV CABs (e.g., establishing one CAB for all ACTIV trials, or having an inpatient trial CAB and an outpatient trial CAB) as well as what entity (e.g., FNIH) will facilitate their activities.

Appendix A: Participants List

WORKING GROUP MEMBERS

Neil Aggarwal, MD, *Lung Biology and Disease Branch Chief, NHLBI*

Sam Bozzette, MD, PhD, *Chief Medical Officer, National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH)*

Timothy G. Buchman, MD, PhD, *Biomedical Advanced Research and Development Authority (BARDA)*

Timothy H. Burgess, MD, MPH, *Captain, Navy, UHSU* **Joan Butterton, MD,** *Associate VP, Clinical Research, Infectious Diseases, Merck & Co.*

Joan Butterton, MD, *Associate VP, Clinical Research, Infectious Diseases, Merck & Co.*

Sylva Collins, PhD, *Director of the Office of Biostatistics, FDA*

Judith Currier, MD, *Professor of Medicine in the Division of Infectious Diseases, University of California, Los Angeles (UCLA)*

Carl Garner, PhD, *VP, Global Regulatory Affairs, Eli Lilly*

Elizabeth (Libby) Higgs, MD, MIA, DTM&H, *Global Health Science Advisor, National Institute of Allergy and Infectious Diseases (NIAID)*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis (WG Co-chair)*

Lisa LaVange, PhD, *Associate Chair, Department of Biostatistics, UNC*

John Mellors, MD, *Professor of Medicine, Chief of Infectious Diseases Division, U. Pittsburgh*

Sandeep Menon, PhD, *Senior VP and Head of Early Clinical Development, Pfizer*

Naimish Patel, MD, *Global Development Head of Therapeutic Area, Immunology and Inflammation, Sanofi*

Amanda Peppercorn, MD, *Senior Medical Director, Infectious Disease, GlaxoSmithKline (GSK)*

Michael Proschan, PhD, *Mathematical Statistician, Biostatistics Research Branch, NIAID, NIH*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH (WG Co-chair)*

Yves Rosenberg, MD, MPH, *Atherothrombosis and Coronary Artery Disease Branch Chief, NHLBI*

Daniel Ruben, PhD, *Division of Biometrics IV, CDER, FDA*

Peter Stein, MD, *Director of Office of New Drugs, CDER, FDA*

INVITED PARTICIPANTS

John Beigel, MD, *Associate Director for Clinical Research, Division of Microbiology & Infectious Diseases, NIAID*

Christine Colvis, PhD, *Director for Drug Development Partnership Programs, NCATS, NIH*

Michelle Culp, MPH, *Office of the Director, NIH*

Ellen Gadbois, PhD, *Office of Science Policy, Office of the Director, NIH*

Mary Groesch, PhD, *NHLBI*

Jacqueline Kirchner, PhD, *Senior Program Officer, Bill and Melinda Gates Foundation*

Hilary D. Marston, MD, MPH, *Medical Officer/Policy Advisor, NIAID, NIH*

John Young, PhD, *Global Head, Infectious Diseases, Roche*

STAFF

Stacey Adam, PhD, *Director, Cancer, Foundation for the NIH (FNIH)*
Michael Santos, PhD, *Associate VP of Science, FNIH*

Helen Q. Chen, PhD, *Senior Consultant, Deloitte*
Rosa Maria Alvarez, PhD*, Consultant, Deloitte*

Lucas Smalldon, MA, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

Timothy Buchman

16:20

Does someone have an update on the enrollment of the baracitinib trial? That may be the last time that we have "SOC" not including a substantial steroid use...

Timothy Buchman

19:29

Thanks; that trial will provide a great deal of helpful information.

Sandeep Menon

34:20

Does the 11 compounds include pre-clinical and clinical stage compounds?

High-Level Meeting Summary

The Preclinical Working Group (WG) discussed prioritizing antivirals for testing, finalizing the NCATS OpenData Portal, connecting researchers with BSL 3/4 facilities, drafting the pandemic response drug development manuscript, and addressing various elements of animal models.

Action Items

- Dr. Menetski will share a clinical master protocol with Drs. Sheri Hild, Haigwood, and Rappaport
- Dr. Menetski will send a list of potential compound testing requirements to the WG
- Dr. Menetski will share the abstract and figures of the manuscripts. WG members should provide feedback and recommendations. Once the first draft is finalized, the pandemic manuscript abstract and figures will also be circulated to the WG for feedback.
- Ms. Samantha Jonson will meet with Drs. Menetski and Rosa Maria Alvarez to discuss the ultimate form in which the animal model summary table will appear on the NCATS portal
- Dr. John Young will inform *Cell Host & Microbe* that the target manuscript length will be 5000 words and include five figures

For Further Discussion

- Further WG discussion will be required to determine the needs and logistics involved in developing a small animal model network.

Antiviral Prioritization

The Preclinical and Therapeutics-Clinical (TX-Clinical) WGs have formalized a common triage and prioritization process for compounds for ACTIV consideration, which will initially focus on identifying antivirals for testing. The triage process removes compounds that are already being tested in parallel efforts as well as compounds that don't have preclinical efficacy data or have not been tested in a multiple ascending dose study. The remaining compounds are evaluated by an expert panel and scored based on compound information such as known mechanisms of action, availability of clinical and preclinical efficacy data, and suitability for specific patient populations. If a compound does not move to the expert panel stage, it may still be considered for future rounds of testing, depending on what supporting data exist or may be obtained for the drug.

Data Portal Implementation

NHP and small animal model data will be iteratively added to the NCATS COVID-19 OpenData Portal as they become available. The WG has provided feedback to NCATS regarding what data to include in the animal model summary tables. These data have been collected and should be uploaded to the portal by the beginning of next week. In addition, the WG will work with the Tulane University NPRC coordinating center to house detailed study-level animal model information (not to be released to the public) and develop data analytic capabilities in the next few months.

BSL 3/4 Network Implementation

ACTIV will leverage the Pandemic Response drug development SOPs to establish requirements to access the BSL 3/4 network for groups developing COVID-19 treatment compounds. It recognizes, however, that these requirements might not be achievable in their entirety by all laboratories ; some labs may prefer to focus on a subset of compound testing requirements, such as studying specific vaccine or antiviral mechanisms, and/or may lack access to BSL 3/4 facilities.

To maximize the number of laboratories included in compound development, the WG will establish a virtual network of scientists and form partnerships between laboratories with complementary needs and capabilities (e.g., BSL 3/4 capabilities). The WG has already established an inventory of BSL 3/4 sites from which it can solicit interest in participating in such a network. Information regarding site capabilities will remain private, however, to enable ACTIV to coordinate the flow and source of requests and avoid overwhelming sites with compound testing requests. When ACTIV connects research groups, it may also provide guidance regarding publication rights (e.g., including a 30-day publication hold in material transfer agreements).

Pandemic Response Manuscript Submission

The WG agreed to pursue the journal *Cell Host & Microbe* for publication of its Pandemic Response Manuscript, with *Clinical and Translational Science* as the secondary option as the editors from both journals have expressed interest in the manuscript. The manuscript will be approximately 5,000 words in length and is likely to include five figures. Initial drafts of all manuscript sections, excluding the conclusion, are complete. WG members will receive the abstract and figures immediately and will receive a full draft of the manuscript when it is ready. Dr. Christine Colvis requested WG feedback to help make the figures as intuitive as possible.

Animal Models

NHP Network

Drs. Nancy Haigwood, Jay Rappaport, and others are developing a nonhuman primate research center (NPRC) SARS-CoV-2 Vaccine & Therapeutic Evaluation Network (CoVTEN). Dr. Haigwood shared a slide detailing CoVTEN's structure, which will include an oversight committee (with both NPRC directors and NIH advisors) that approves compounds for testing, an operations leadership group that prioritizes compounds and facilitates their testing, a coordinating center (housed at Tulane University) that manages data sharing, tissue storage, and protocol and assay distribution, and a unit made up of the NPRCs that evaluates COVID-19 vaccines and therapeutics. The ACTIV Preclinical WG will assist the coordinating center with its remit and ensure that CoVTEN addresses the ACTIV Preclinical and TX-Clinical WGs' needs for compound testing in NHPs.

Small Animal Virtual Network

The WG plans to create a virtual network of small animal research sites and make compound data produced by this network publicly available on the NCATS portal. Because many researchers may be reluctant to share data publicly, the WG may limit data sharing to NIH contracted research and existing public repositories (e.g., bioRxiv). ACTIV may also consider soliciting colleagues to conduct assays on publicly available small animal models in order to deliberately generate public data that will likely spur further compound research. Making small animal model testing data publicly available will allow the research community to identify gaps and avoid redundant data collection.

Cross-Species Comparisons and Parallel Testing of Animal and Human Tissue

Dr. Joe Menetski reviewed a list of measures that the WG may require NHP therapeutic and vaccine researchers (and, ideally, human and small animal researchers) to conduct during compound testing to enable cross-species comparisons. These measures include genetics assays (e.g., genome, exome, and viral sequencing), laboratory measures (e.g., cytokine profiling, immune phenotyping, and RNA-seq), and clinical measures (e.g., blood pathology, peripheral physiology, and tissue assays). The WG will need to prioritize the elements on the list so that it promotes efficacious compound testing without overburdening laboratories with excessive testing requirements; it will not be feasible to require collection of every item. Dr. Rappaport noted that the use of wearable devices to record biometrics such as ECG, respiration, and blood oxygen level may speed NHP testing by avoiding implantation surgeries and the time to recover from them; pilot testing of these devices will occur shortly.

A laboratory at Stanford University plans to obtain NHP tissue samples from NPRCs and human tissue samples from clinical sites to conduct parallel tissue assays for cross-species comparisons. WG members may coordinate similar studies that involve concurrent testing of a circumscribed set of compounds using human and small animal tissue. Such testing can improve existing animal models and potentially identify models that approximate human sequelae (e.g., ARDS and pneumonia). Because small animal models are not resource-limiting, the development of informative small animal models can also reduce the testing load being placed on NPRCs.

Next Steps

Dr. Menetski will share a clinical master protocol with Drs. Sheri Hild, Haigwood, and Rappaport, and send a list of potential compound testing requirements to the WG. The pandemic manuscript abstract and figures will also be circulated to the WG for feedback. Ms. Samantha Jonson will meet with Drs. Menetksi and Rosa Maria Alvarez to discuss the ultimate form in which the animal model summary table will appear on the NCATS portal. Dr. John Young will inform *Cell Host & Microbe* that the target manuscript length will be 5000 words and include five figures. Further WG discussion will be required to determine the needs and logistics involved in developing a small animal model network.

Appendix A: Participants List

WORKING GROUP MEMBERS

Peter Adams, PhD, *Health Scientist, Project Officer, BARDA*

Annaliesa Anderson, PhD, (not in attendance) *Vice President and CSO Bacterial Vaccines, Pfizer*

Ralph Baric Professor, PhD, (not in attendance) *Dept. of Epidemiology and Dept. of Micobiology and Immunology, UNC Chapel Hill*

Kara Carter, PhD, *Senior Vice President Infectious Disease, Evotec*

Marc Charette, PhD, *Division of Cardiovascular Diseases NIH, NHLBI*

Tomas Cihlar, PhD, *VP, and Head of Virology, Gilead*

Christine Colvis, PhD, *Director, Drug Development Partnership Programs, NCATS*

Damon Deming, PhD, (not in attendance) *Virologist, Division of Antiviral Products, Office of New Drugs, FDA*

Michael Diamond, MD, PhD, *Professor, Depts. of Medicine, Molecular Microbiology, Pathology & Immunology, Washington University*

Ken Duncan, PhD, *Gates Foundation*

Prabhavathi Fernandes, PhD, (not in attendance) *Retired, most recently led biotechs Cempra and DarPharma*

Josh Fessel, MD, PhD, *Division of Lung Diseases NIH, NHLBI*

Clint Florence, PhD, *Program Officer, Research Resource Section, OBRR, DMID, NIAID*

Greg Gatto, PhD, *Drug Development Regulatory Project Leader, RTI*

Jay Grobler, PhD, *Director, Infectious Disease Biology, Merck*

Nancy Haigwood, PhD, *Director and Professor, Oregon National Primate Research Center, OHSU*

Judith Hewitt, PhD, *Deputy Director, Office of Biodefense, Research Resources and Translational Research, NIAID*

Samantha Jonson, MPS, *Special Assistant to the Director, NCATS*

Cat Lutz, PhD, *Senior Director, Mouse Repository & In Vivo Pharmacology, Rare and Orphan Disease Center, Jackson Laboratory*

Frank Nestle, MD, (not in attendance) *Global Head of Immunology Therapeutic Research Area and Chief Scientific Officer North America, Sanofi*

Liz Ottinger, PhD, *Project Manager, NCATS*

David Payne, PhD, DSc, (not in attendance) *Vice President & Head, Medicine Opportunities Research Unit, GSK*

Louise Pitt, PhD, *Director, Center for Aerobiological Sciences, USAMRIID*

Tony Punturieri, MD, PhD, *Division of Lung Diseases NIH, NHLBI*

Srinivas Rao, MBA, PhD, *Global Head Translational In Vivo Models, Sanofi*

Jay Rappaport, PhD, *Director and Chief Academic Officer, Tulane Primate Center*

John Young, PhD, *Global Head Infectious Diseases and Vice President, Roche*

INVITED PARTICIPANTS

Michelle Culp, MPH, *Senior Policy Advisor, NIH*

Sheri Hild, PhD, *Program Director for the National Primate Research Centers (NPRCs) at Office of Research Infrastructure Programs, NIH*

Felicia Qashu, PhD, *Program Officer at National Institutes of Health*

FNIH STAFF

Stacey Adam, PhD, *Director, Cancer, Research Partnerships, FNIH*

Joseph P. Menetski, PhD, *Associate VP of Research Partnerships, FNIH*

Michael Santos, PhD, *Associate Vice President, Science, FNIH*

Rosa Maria Alvarez, PhD, *Senior Consultant*, *Monitor, Deloitte*

Benjamin Stratton, PhD, *Senior Consultant, Deloitte*

David Frankowski, PhD*, Writer, Rose Li and Associates, Inc*

Appendix B: Chat Transcript

From Srinivas Rao to Everyone: 10:13 AM

I see CT is not on this list, even though it is perhaps a "nice to have"

From Haigwood to Everyone: 10:14 AM

It used to be on the list, sorry dropped off. Other assays we are missing?

From Srinivas Rao to Everyone: 10:15 AM

Microneut or Pseudotyped viral assays. I only see PCR. That should be a must have

From Haigwood to Everyone: 10:16 AM

Neutralization is listed under adaptive responses

From Srinivas Rao to Everyone: 10:16 AM

ah, okay Nancy. Thanks

From Tony P to Everyone: 10:17 AM

Is measurement of NK activity also a drop?

From Haigwood to Everyone: 10:19 AM

Good catch on NK

From Kara Carter to Everyone: 10:21 AM

It might be useful to have a chart of NHP endpoints/assays and those from the clinical protocols

From hildsa to Everyone: 10:22 AM

Kara, agree alignment of the preclinical and clinical endpoints would be very helpful.

From Jay Rappaport to Everyone: 10:24 AM

We can do this for therapeutics, antibodies, and vaccines

From christine.colvis@nih.gov to Everyone: 10:55 AM

I'm sorry. I have a hard stop at 11.

From Joseph Menetski to Everyone: 11:02 AM

Ok, stopping now

High-Level Meeting Summary

The Therapeutics-Clinical Working Group (TX-Clinical WG) reviewed outcomes from the June 17 ACTIV Executive Committee (EC) meeting and heard updates from its Master Protocol Subgroup (MPSG) and Agent Prioritization Subgroup (APSG). The WG also viewed a demonstration of the Clinical Trial Capacity (CTC) WG's GeoTracking Dashboard.

Executive Committee Meeting Updates

The EC responded well to TX-Clinical WG Co-Chairs' presentations during its June 17 meeting. Dr. Francis Collins suggested that the ACTIV-2 team and the Vaccines WG coordinate efforts to ensure sufficient patient enrollment in their trials, because recruitment of outpatients and of healthy individuals face similar challenges (i.e., attracting volunteers to healthcare sites they have been advised to avoid during the pandemic) and will focus on similar geographic areas (i.e., those where the virus is currently spreading). Drs. Stacey Adam and Sarah Read will coordinate invitations to ACTIV-2 and ACTIV-3 members for tomorrow's Vaccines WG call.

EC members also recommended that the ACTIV-2 master protocol team, and potentially other protocol teams, coordinate with NIH's Rapid Acceleration of Diagnostics for Underserved Populations (RADx-UP) team to address trial recruitment challenges. They also stressed the need to examine the RECOVERY study results to identify any potential implications for ACTIV master protocol designs (see below for an update on ACTIV-1).

Dr. Collins, following up on the TX-Clinical WG's May letter to the EC about inventorying global efforts against COVID-19 and establishing a data sharing platform, also provided updates that (1) the HEVER Group continues to grow its inventory of efforts against COVID-19, which will be shared as soon as it is available, and (2) conversations are ongoing to synergize data platforms that provide analytics of trial summary data (e.g., the (b)(4) [redacted] platform) and those that securely capture individual patient-level data (e.g., the TransCelerate platform).

Neutralizing mAb Clinical Summit Follow-Ups

Since the June 9 Neutralizing mAb Clinical Summit, the TX-Clinical WG has been confirming mAb trial governance structure. The Trial Oversight Committee will begin meeting next week and the Agent Selection Committee (ASC) will begin meeting this week to review any data submitted by companies through the Agent Survey Portal (data will be assessed against Neutralizing Antibody Minimal Entry Criteria). The two Protocol Leadership Committees (for ACTIV-2 and ACTIV-3) are mostly formed and will be refreshed as new companies are onboarded.

Master Protocol Subgroup Updates

The MPSG presented on the status of its various master protocols now under development:

- ACTIV-1 (phase III; immunomodulators; inpatients; projected July launch)
- ACTIV-2 (phase II/III; neutralizing mAbs; outpatients; projected July launch)
- ACTIV-3 (phase II/III; neutralizing mAbs; inpatients; projected July launch)

- ACTIV-4 (phase III; anticoagulants; inpatients; projected June launch)

ACTIV-1: Immunomodulators (Inpatient Phase III)

The ACTIV-1 master protocol document is near complete. In discussion with Janssen, Bristol Myers Squibb, and AbbVie/Allergan representatives, the team considered the implications of the RECOVERY study results for ACTIV-1 study design and decided to forego making significant changes until additional data become available. NIAID's Division of Allergy, Immunology, and Transplantation (DAIT) conducted its Clinical Research Policies and Standards (CRPS) review of the trial design and operational plan and will decide over the next several days whether it will sponsor the trial. The ACTIV-1 team has also engaged with NCATS' Trial Innovation Network (TIN) to oversee operational planning and trial implementation. Next week, the TIN will host a webinar to recruit sites to participate in the trial. Next steps are to update the master protocol based on DAIT feedback; finalize trial sponsor, network, and CRO; and submit a Pre-IND to FDA.

Discussion

Participants acknowledged that, given the results from RECOVERY and other studies of steroids, the standard of care is likely to change over the next few weeks—with potential implications for the ACTIV-1 trial design. The MPSG will is prepared to adjust the protocol as needed (e.g., it will conduct a blinded sample size re-estimation if necessary to adjust for blunted signal for new agents due to this new combination).

ACTIV-2: Monoclonal Antibodies (Outpatient, Phase II/III)

The ACTIV-2 writing team has received comments from FDA on its Pre-IND submission and is responding to those comments in developing Version 1.0 of the master protocol; simultaneously the statistics team continues to run simulations for ACTIV-2's Bayesian learning method, and NIAID's Division of AIDS (DAIDS) is coordinating with PPD (a CRO) to execute trial implementation. The ACTIV-2 operations team has liaised with the All of Us organization to discuss strategies for recruitment of outpatients for the trial, especially in underserved populations. Next steps are to update the protocol as needed and submit a New IND to FDA; launch a public relations campaign to ensure successful patient enrollment; and continue to plan for protocol implementation.

ACTIV-3: Monoclonal Antibodies (Inpatient, Phase II/III)

The ACTIV-3 writing team finished addressing comments from DAIDS' Clinical Science Review Committee (CSRC) and on June 17, 2020 submitted the updated protocol to FDA for its Pre-IND review. The Agent Selection Committee formally approved (b) (4) to enter its mAb into ACTIV-3 (representatives of (b) (4) have joined the trial's writing and operations teams); (b) (4)

(b) (4)

(b) (4) The INSIGHT team continues to work with the PETAL, CTSN, and VA teams to coordinate trial implementation and has identified operational capability gaps to be filled by a CRO. Next steps are to receive and respond to comments from FDA on the Pre-IND submission, develop an agent-specific appendix to the protocol in collaboration with (b) (4) representatives, and continue to plan for protocol implementation. DSMB review of ACTIV-2 and ACTIV-3 is scheduled for June 29.

ACTIV-4: Anticoagulants (Inpatient, Phase III)

Following extensive external review, the ACTIV-4 master protocol has been finalized. It will soon undergo DSMB review and upon approval will immediately begin enrollment. Approximately 15 clinical trial networks are poised to participate in ACTIV-4. Dr. Andrei Kindzelski will send to Dr. Adam descriptions of the interventions that will be tested and she will circulate them to appropriate ACTIV members.

Agent Prioritization Subgroup Updates

The APSG has established its Antivirals Subteam, which is coordinating with the Preclinical WG in preparation for Wave 2 and will begin this week to evaluate and prioritize approximately 80 candidate antiviral agents. In addition to conducting Wave 2 agent prioritization, next week the APSG will assemble prioritization subteam for host-targeted compounds/ immunomodulators therapies. The APSG continues to collect both preclinical and clinical data on candidate agents through the ACTIV Compound Survey, and as of June 17, 2020 had received 24 submissions. It will circulate data to the mAb Agent Selection Committee and the other agent prioritization subteams to evaluate.

Clinical Trial Capacity Dashboard Demo

Dr. Karen Tountas and Mr. Jonathan Wachtel demonstrated the CTC WG's Clinical Trial Capacity GeoTracking Dashboard, which contains geographic mappings of data from the CTC WG's surveys of clinical trial networks and sites, CROs, and site management organizations (SMOs), as well as Johns Hopkins University's COVID-19 case tracking data. The CTC WG is leveraging this tool to help identify optimal networks, sites, and CROs/SMOs to execute each ACTIV trial (e.g., using information such as site enrollment capacity). Dr. Lisa LaVange proposed that the tool include a feature allowing users to filter networks and sites by patient population *type* to help match networks' and sites' patient populations with those targeted by each master protocol.

The Dashboard is available to anyone who is involved in ACTIV, which includes (1) staff working on COVID-related efforts at companies that are ACTIV Leadership members with the intent of public health benefit and/or to eliminate duplication of efforts; (2) individuals working on the development and/or execution of ACTIV-branded clinical trials; or (3) staff involved in COVID-related efforts at organizations coordinating and/or aligning with ACTIV for public health benefit and/or to eliminate duplication of efforts. Those interested in gaining access can email Dr. Adam. Mr. Wachtel will email Dr. Adam instructions to help ACTIV members create a user account. Dr. Jacqueline Kirchner will connect the CTC Dashboard development team with representatives of (b) (4) [redacted], who are working on similar efforts.

Appendix A: Participants List

WORKING GROUP MEMBERS

Neil Aggarwal, MD, *Lung Biology and Disease Branch Chief, NHLBI*

Sam Bozzette, MD, PhD, *Chief Medical Officer, National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH)*

Timothy G. Buchman, MD, PhD, *Biomedical Advanced Research and Development Authority (BARDA)*

Timothy H. Burgess, MD, MPH, *Captain, Navy, UHSU* **Joan Butterton, MD,** *Associate VP, Clinical Research, Infectious Diseases, Merck & Co.*

Judith Currier, MD, *Professor of Medicine in the Division of Infectious Diseases, University of California, Los Angeles (UCLA)*

Angelo DeClaro, MD, *Division Director (Acting), Division of Hematologic Malignancies, Food and Drug Administration (FDA)*

Ruxandra Draghia-Akli, MD, PhD, *Global Head, Global Public Head R&D, Johnson & Johnson*

Mark Eisner, MD, MPH, *Senior VP, Global Head of Immunology, Infectious Disease, and Ophthalmology Clinical Development, Genentech*

Carl Garner, PhD, *VP, Global Regulatory Affairs, Eli Lilly*

Elizabeth (Libby) Higgs, MD, MIA, DTM&H, *Global Health Science Advisor, National Institute of Allergy and Infectious Diseases (NIAID)*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis (WG Co-chair)*

Andrei Kindzelski, MD, PhD, *Program Director, Division of Blood Diseases and Resources, National Heart, Lung, and Blood Institute (NHLBI)*

Lisa LaVange, PhD, *Associate Chair, Department of Biostatistics, UNC*

John Mellors, MD, *Professor of Medicine, Chief of Infectious Diseases Division, U. Pittsburgh*

Michael Proschan, PhD, *Mathematical Statistician, Biostatistics Research Branch, NIAID, NIH*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH (WG Co-chair)*

Lora Reineck, MD, *Program Director, Lung Biology and Disease Branch, NHLBI*

Yves Rosenberg, MD, MPH, *Atherothrombosis and Coronary Artery Disease Branch Chief, NHLBI*

Daniel Ruben, PhD, *Division of Biometrics IV, CDER, FDA*

Peter Stein, MD, *Director of Office of New Drugs, CDER, FDA*

INVITED PARTICIPANTS

Christine Colvis, PhD, *Director for Drug Development Partnership Programs, NCATS, NIH*

Michelle Culp, MPH, *Office of the Director, NIH*

Mary Groesch, PhD, *NHLBI*

Hilary D. Marston, MD, MPH, *Medical Officer/Policy Advisor, NIAID, NIH*

Ashley Parker, PhD, *Health Science Policy Analyst, NIH*

Allan Shipp, MHA, *Senior Clinical Research Policy Analyst, Office of Science Policy, NIH*

John Young, PhD, *Global Head, Infectious Diseases, Roche*

STAFF

Stacey Adam, PhD, *Director, Cancer, Foundation for the NIH (FNIH)*
Joseph P. Menetski, PhD, *Associate VP of Research Partnerships, FNIH*
Karen Tountas, PhD, *Scientific Program Manager, FNIH*
David Wholley, MPhil, *Senior VP of Research Partnerships, FNIH*

Helen Q. Chen, PhD, *Senior Consultant, Deloitte*
Jonathan Wachtel, *Manager, Deloitte*

Lucas Smalldon, MA, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

Timothy Buchman: 13:26

Thank you so much for these updates.

Timothy Buchman: 16:04

Speaking in another one of my roles as Editor-In-Chief of a major journal, the importance of data sharing or at least a verification strategy for data in databases cannot be overstated.

Timothy Buchman: 22:10

For those interested in seeing how physicians are mixing steroids and immunomodulators, please see https://journals.lww.com/ccejournal/Fulltext/2020/06000/The_Combination_of_Tocilizumab_and.23.aspx

Ruxandra Draghia-Akli: 39:39

Could we have the presentation? It is a bit small on the screen....

Ruxandra Draghia-Akli: 40:00

Thank you very much.

(b) (6) **45:48**

@Jonathan: sorry if I missed it but what do you mean by capacity?

Timothy Buchman: 48:52

What a superb tool to understand sites and cases!

Carl's Lilly iPad: 51:50

This is outstanding. Goodwork! Have you done an overlay with Rt values?

Carl's Lilly iPad: 52:18

Might help skate to the puck

Joan Butterton: 54:22

Yes, agree with Carl!

Andrei Kindzelski: 55:18

Who is expected to have access to this resource?

Karen Tountas: 01:00:06

Many thanks to Jonathan and the dashboard team at Deloitte for creating a super useful tool! I and the capacity working group have enjoyed working with them on this.

Timothy Buchman: 01:00:31

Echoing: "Bravo!"

(b) (6) **01:01:06**

Echoing the echo: bravo!

Andrei Kindzelski: 01:01:40

Excellent resource! Thank you.

High-Level Meeting Summary

The Therapeutics-Clinical (TX-Clinical) Working Group (WG) received status updates from the Master Protocol Subgroup (MPSG), including progress on ACTIV-6, and the Agent Prioritization Committee (APC), as well as an overview of the proposed biospecimen prioritization process for secondary research with ACTIV clinical samples.

Master Protocol Subgroup Updates

The MPSG reviewed progress on its various master protocols (ACTIV-1/-2/-3/-4/-5):

ACTIV-1: Immunomodulators (Inpatient Phase III)

ACTIV-1 has activated 38 sites, including five satellite sites, and randomized 356 participants. The demographic distribution of accrued participants continues to be balanced. The ACTIV-1 team has selected 87 additional sites (62 U.S. and 25 ex-U.S.) and has received regulatory approval in Argentina, Brazil, and Peru. Co-enrollment with ACTIV-4A is still on hold, pending protocol revisions requested by the National Heart, Lung, and Blood Institute (NHLBI). The team is also evaluating (b) (4)) sub-study challenges and staffing needs.

Discussion

Two agents referred to ACTIV-1 have been deferred at this time due to lack of capacity. The ACTIV-1 team will review its capacity for additional agents after futility analysis for the first three agents is complete.

Dr. Ruxandra Draghia-Akli asked whether the team would consider sample size re-estimation based on recent data suggesting effect sizes may be smaller than anticipated. At present, those discussions have been limited to an oral agent administered in the acute setting, for which sample size may be recalculated if use is restricted to only patients with moderate disease. ACTIV-1 has not reached its accrual milestone for sample size re-estimation.

The ACTIV-1 team is responding to FDA comments about its statistical analysis plan. FDA expressed concerns about a potential conflict between the primary endpoint, time to recovery, and the secondary endpoint, mortality. However, the ACTIV-1 team wants to retain the DSMB decision based on 29-day data. Mortality will be assessed, but statistical power will likely be lower because the base rate of mortality events is not expected to be high.

ACTIV-2: Monoclonal Antibodies (Outpatient, Seamless Phase II/III)

ACTIV-2 has activated 104 sites and (b) (4) in total between Versions 1.0 and 2.0 of the master protocol. Version 1.0, with the (b) (4) agent, closed for all sites as of January 15. Version 3.0, which includes agents from (b) (4) (both IM and infused), (b) (4) enrolled its first patient yesterday. A letter of amendment (LOA) has been submitted for Version 3.0 to avoid the pause between Phase II and Phase III of the protocol. Version 4.0, including the SAb polyclonal antibody (pAb), is under review by CBER and is expected to launch in late February after issues with SAb's chemistry, manufacturing, and control (CMC) data are resolved. The ACTIV-2 team is working on Version 5.0 of the master protocol, with (b) (4) agents. The team will determine capacity for additional agents (e.g., for a protocol Version 6.0) after current agents clear the study pipeline.

Recruitment of African American participants continues to be slow. The team is leveraging faith-based outreach systems and minority-owned barbershops to improve African American enrollment. The ACTIV-2 team is meeting with FDA today to discuss a proposed symptomatic endpoint for future Versions of the protocol. Both ACTIV-2/-3 are developing sub-studies to evaluate the effects of monoclonal antibody (mAb) therapeutics on vaccine efficacy, with trial teams meeting to harmonize those efforts.

Discussion

Dr. Stacey Adam noted ACTIV-2 is collecting patient samples to track efficacy against emerging viral strains for all therapeutic agents. Those data are not yet tracked in real-time, but a recent study demonstrated that several of the prevalent mAb cocktails, including (b) (4) cocktail, retain efficacy against the UK, South African, and Brazil variants. In addition, USG is independently testing ACTIV agents against emerging viral variants in vitro. ACTIV-2 is discussing real-time examination of efficacy against SARS-CoV-2 variants in the future for patients whose viral loads do not respond to treatment.

ACTIV-3: Monoclonal Antibodies (Inpatient, Seamless Phase II/III)

ACTIV-3 previously activated 60 sites, including six ex-U.S. sites, and (b) (4) into Version 2.0, with agents from (b) (4) and (b) (4). ACTIV-3 is now activating new sites and transitioning current sites to Version 3.0. Enrollment is expected to increase as more ex-U.S. sites are activated. However, overall demographics will be skewed as international enrollment increases. The ACTIV-3 team is having difficulty finding available vaccine for its sub-study evaluating the effects of mAb therapeutics on vaccine response.

Follow-up for patients receiving (b) (4) is complete, with data analysis for baseline antibody and viral load expected to be complete next week. Version 2.0 launched in December, and two DSMB safety reviews were held in January 2021, after (b) (4) were enrolled to each arm. The next DMSB meeting will be a futility review, at which point (b) studies will end. If futility is demonstrated, ACTIV may need to reconsider the use of mAbs in the inpatient setting. Dr. Libby Higgs noted ACTIV-3 was previously asked by FDA to not enroll patients on high-flow oxygen because data from other studies indicated a harm signal.

Discussion

Dr. Revell Phillips noted the Defense Threat Reduction Agency (DTRA) is considering a study to evaluate mAb effects on vaccine response, similar to the ACTIV-2/-3 sub-studies. Dr. Higgs considered harmonization with the ACTIV-2 sub-study protocol, which has already been through internal and FDA review, to be essential. Dr. Adam offered to contact Dr. Davey Smith about sharing the ACTIV-2 protocol with DTRA to avoid duplication of effort.

ACTIV-4: Anticoagulants (Pre-hospitalized/Hospitalized/Post-hospitalized, Phase III)

ACTIV-4A (hospitalized) remains paused pending approval of the next agents, P2Y12 inhibitors. The therapeutic heparin dose in moderate hospitalized patients and prophylactic heparin dose in severe patients will be maintained as controls, resulting in four study arms. All (b)(4) enrolled prior to the study's pause are still being monitored, data analysis is ongoing, and the study team plans to submit its first manuscript for publication by the end of the week.

ACTIV-4B (pre-hospitalized) has activated 20 sites and (b)(4). Yesterday, ACTIV-4B enrolled its first patient using the novel CVS recruitment pathway, a "touchless" randomized outpatient clinical trial. Dr. Andrei Kindzelski reviewed key steps in this "touchless" approach: (1) the patient was identified and contacted by CVS via phone; (2) the patient was transferred to a research call center in Illinois and consented electronically using the University of Pittsburgh REDCap system; (3) patient data was transferred to Socar Research in Switzerland for electronic data capture (EDC), resulting in the generation of a randomized patient identifier and matching shipping label; (4) the double-blinded study drug or placebo was shipped overnight to the patient by the drug shipping group in Boston; and (5) a home nurse request will be generated and dispatched through Quorum Health to collect the patient's blood sample, which will be stored by Covance Labs with any results sent electronically to Brigham and Women's Hospital. This recruitment pathway is being piloted in Massachusetts and Illinois, after which it will expand to all 50 states. Dr. Kindzelski acknowledged Dr. Adam for facilitating communications with CVS and the NHLBI CONNECT network for contracting support.

ACTIV-4C (post-hospitalization) received safe-to-proceed from both the ACTIV-4 DSMB and FDA. The team is anticipating enrollment of the first patient imminently.

ACTIV-5: Big Effect Trial (Inpatient, Phase II)

ACTIV-5 has activated 13 sites and (b)(4). The ACTIV-5 team continues to identify new sites for future big effect trials (BETs). Two arms are open: (1) BET-A with Risankizumab, an IL-23 inhibitor and (2) BET-B with Lenzilumab, a granulocyte macrophage stimulating factor inhibitor. An agent has been selected for BET-C and the team will continue to review agents for BET-D.

Progress Update for ACTIV-6

ACTIV-6 is an outpatient, pragmatic platform trial to definitively evaluate widely available generic drugs repurposed for COVID-19 treatment. The ACTIV-6 master protocol will have clear endpoints, use a low-touch model, and rely on updated existing prioritization criteria for repurposed generic agents. PCORnet, the lead network, is developing Version 1 of the master protocol with ivermectin as the first agent, and ACTIV has secured an industry sponsor to provide ivermectin and matching placebo. Next steps include recruiting a new agent prioritization subteam to review candidate generic agents. All agents will have a matching placebo; however, because all agents are oral, patients will be randomized to a grouped placebo arm to maximize the number of participants who can be randomized to the treatment arms.

Discussion

Three ACTIV-6 endpoints are under consideration: (1) hospitalization, (2) disease progression, and (3) some type of symptomatic improvement. Dr. Walter Koroshetz recommended *time to resolution of symptoms* as a primary outcome because it will likely require fewer participants. The key concern about this endpoint for an outpatient population is variance in clinical interpretation of "resolution of symptoms," which could complicate the power analysis. However, progression-based endpoints restrict the effective number of study participants, potentially increasing target enrollment and impacting feasibility of the study. Dr. Koroshetz offered to find data from UK studies comparing symptomatic to more traditional endpoints.

Agent Prioritization Updates

Dr. Adam provided a summary for Waves 2 and 3 of agent prioritization. She noted that a new antiviral protease inhibitor from Pfizer has received approval to move forward with the ACTIV-3 study team. However, the agent is delivered by continuous infusion, likely limiting its utility to the inpatient population. In addition, Aviptadil (i.e., vasoactive intestinal peptide [VIP]) has been approved for ACTIV-3B, a factorial study with (b)(4) That study may have capacity for additional agents in patients with acute respiratory distress syndrome (ARDS).

ACTIV Biospecimen Prioritization

ACTIV leadership requested that the use of residual samples be coordinated across ACTIV trials in order to best leverage these samples for valuable science. Dr. Adam reviewed the current proposed prioritization plan, which has been vetted with the ACTIV trial teams. The ACTIV Biospecimen Prioritization Committee (ABPC) will be established to evaluate, prioritize, and approve secondary research requests for access to residual biospecimens, ensuring that their use will accelerate COVID-19 research by addressing the most significant scientific questions and contributing scientific and clinical insights to generate maximum clinical impact.

ACTIV Biospecimen Prioritization Committee

The ABPC will be responsible for defining evaluation guidelines for biospecimen requests; collecting, evaluating, prioritizing, and approving requests; and communicating review decisions. The ABPC will not be responsible for non-scientific considerations (e.g., regulatory, legal, financial, and contractual requirements); management and facilitation of biospecimen collection, processing, storage, retrieval, or dissemination; or managing the use of samples for assays in ACTIV studies. To ensure unbiased and comprehensive evaluation of biospecimen requests, the ABPC will include trial representatives, academic experts, and industry partners.

General guidelines for evaluating biospecimen requests include *agreement to NIH guidelines of use* (i.e., the requesting investigator agrees to share research outcomes on the requested biospecimen) because ACTIV is a public-private partnership; clear *research focus* supported by a strong rationale that is intended to advance scientific and clinical understanding to improve public health outcomes; appropriate *experimental design* (e.g., sufficient power, well-planned); and the *credibility of the investigator*, including adequate funding and institutional support. Core responsibilities of the ABPC will be divided amongst *three* committees: (1) the Oversight

Committee, comprised of trial sponsors (e.g., NIAID, NCATS, NHLBI); (2) the Review Committee, comprised of ACTIV trials representatives, academic experts, and industry partners; and (3) Project Management (PM). ACTIV will serve as PM initially and transfer responsibilities to NIH Institute/Centers (ICs) after initial committees and priorities are set because ICs have direct access to ACTIV trials. The ABPC will adopt a streamlined process for consistent, transparent, and timely evaluation of biospecimen requests:

- ***Request Submission*** – external investigators will submit requests via a standardized application through an online portal;
- ***Offline Review*** – PM will manage a bi-weekly review cycle based on pre-defined prioritization criteria;
- ***Group Adjudication*** – PM will facilitate bi-weekly adjudication by the Review Committee and forward the Review Committee's recommendation to the Oversight Committee;
- ***Decision Sign-Off*** – PM will convene a bi-weekly meeting of the Oversight Committee for final decisions on biospecimen requests and formally communicate decisions to the Review Committee and external investigators. For approved requests, PM will facilitate introductions between external investigators and the appropriate ACTIV trial team(s).

The TX-Clinical WG had no further recommendations or considerations for the Biospecimen Prioritization Process or the ABPC. The concept will move forward to ACTIV leadership for final approval. Dr. Adam anticipates that ACTIV will solicit TX-Clinical WG members to join the ABPC after final approval is received.

Appendix A: Participants List

WORKING GROUP MEMBERS

Neil Aggarwal, MD, *Lung Biology and Disease Branch Chief, National Heart, Lung, and Blood Institute (NHLBI)*

Jeremy Brown, MD, *Director, Office of Emergency Care Research, National Institute of Neurological Disorders and Stroke (NINDS)*

Timothy G. Buchman, MD, PhD, *Biomedical Advanced Research and Development Authority*

R. Angelo DeClaro, MD, *Division Director (Acting), Division of Hematologic Malignancies, Food and Drug Administration (FDA)*

Ruxandra Draghia-Akli, MD, PhD, *Global Head, Global Public Head R&D, Johnson & Johnson*

Keith Gottesdiener, MD, *Former President and Chief Executive Officer, Rhythm*

Elizabeth (Libby) Higgs, MD, MIA, DTM&H, *Global Health Science Advisor, National Institute of Allergy and Infectious Diseases (NIAID)*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis (WG Co-chair)*

Andrei Kindzelski, MD, PhD, *Program Director, Division of Blood Diseases and Resources, NHLBI*

Walter Koroshetz, MD, *Director, NINDS*

Lisa LaVange, PhD, *Professor and Associate Chair, Department of Biostatistics, UNC Chapel Hill*

John Mellors, MD, *Professor of Medicine, Chief of Infectious Diseases Division, University of Pittsburgh*

Michael Proschan, PhD, *Mathematical Statistician, Biostatistics Research Branch, NIAID*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID (WG Co-chair)*

Yves Rosenberg, MD, MPH, *Atherothrombosis and Coronary Artery Disease Branch Chief, NHLBI*

Larry Tsai, MD, *Global Head of Respiratory and Rheumatology Product Development, Genentech*

INVITED PARTICIPANTS

Timothy H. Burgess, MD, MPH, *Captain, Navy*

Christine Colvis, PhD, *Director, Drug Development Partnership Programs, National Center for Advancing Translational Sciences (NCATS)*

Ellen Gadbois, *Program Lead, Emerging Biotechnology Policy, NIH Office of Science Policy*

Dave Hone, PhD, *Chief Scientist, Vaccine and Therapeutic Division, Defense Threat Reduction Agency (DTRA)*

Jacqueline Kirchner, PhD, *Senior Program Officer, Bill and Melinda Gates Foundation*

Andrea Lerner, MD, MS, *Medical Officer, Office of the Chief of Staff, NIAID*

Joanne Lumsden, PhD, *Senior Scientific Program Manager, Drug Development Partnership Programs, NCATS*

Robert Malone, MD, *Chief Medical Officer, Alchem Laboratories Corporation*

Ashley Parker, PhD, *Health Science Policy Analyst, NIH*

Martha Petrovick, *MIT Lincoln Laboratory*

Revell Phillips, PhD, *Science and Technology Manager, DTRA*

Lora Reineck, MD, *Program Director, Lung Biology and Disease Branch, NHLBI*
Ronald Reisler, MD, MPH, *Senior Clinical Advisor, Davis Defense Group*
Christine Sizemore, PhD, *Director, Division of International Relations, Fogarty International Center, NIH*

STAFF

Stacey Adam, PhD, *Director, Cancer, Foundation for the NIH (FNIH)*
David Wholley, MPhil, *Senior VP of Research Partnerships, FNIH*

Evan Appell, *Consultant, Deloitte*
Helen Chen, PhD, *Consultant, Deloitte*
Hana Nasr, *Consultant, Deloitte*
Alex Sorosa, *Business Analyst, Deloitte*

Kelly E. Beazley, PhD, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

Libby Higgs to Everyone: 12:22 PM

So far mAbs in ACTIV 2 and ACTIV 3 are holding up in the pseudo neutralization assays. Waiting on the LVNA out in the next few weeks from the NIAID IRF.

Stacey Adam to Everyone: 12:22 PM

Terrific!

Timothy Buchman to Everyone: 12:24 PM

Wonderful to hear. There are discrepant recommendations coming from various authorities on the use of monoclonals (see for example IDSA current guidance) more information will be helpful to resolve same.

Timothy Buchman to Everyone: 12:28 PM

Simply for reference compare https://www.idsociety.org/covid-19-real-time-learning-network/therapeutics-and-interventions/monoclonal-antibodies/

Timothy Buchman to Everyone: 12:28 PM

and https://combatcovid.hhs.gov/i-have-covid-19-now/monoclonal-antibodies-high-risk-covid-19-positive-patients

Timothy Buchman to Everyone: 12:29 PM

and also the updated IDSA information here https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/

Revell Phillips DTRA to Everyone: 12:29 PM

Can we get more information on how you are examining the vaccine response?

Stacey Adam to Everyone: 12:34 PM

YAY!!!!

Neil Aggarwal to Everyone: 12:34 PM

That is fantastic news!

Sarah Read to Everyone: 12:37 PM

Congratulations!!

Eric Hughes to Everyone: 12:37 PM

Yahoo!! :-)

Timothy Buchman to Everyone: 12:37 PM

BRAVO!

Timothy Buchman to Everyone: 12:38 PM

Public Private Partnerships are foundational!

Revell Phillips DTRA to Everyone: 12:46 PM

PCR results?

Robert Malone to Everyone: 12:47 PM

Key question for time to event resolution of symptoms in outpatients is a standardized scale for symptom severity that has been validated.

Neil Aggarwal to Everyone: 12:47 PM

Might be hard to operationalize with a pragmatic study, depending on how light-touch the intent is to be in activ-6.

Robert Malone to Everyone: 12:49 PM

DTRA/JSTO is grappling with this same question in outpatient population. We are intending to drop this into exploratory because of lack of validated symptom scale.

Stacey Adam to Everyone: 12:49 PM

Thanks, Robert, helpful.

Robert Malone to Everyone: 12:50 PM

If ACTIV/FNIH can establish a validated symptom scale this would be very helpful.

tburgess to Everyone: 12:50 PM

We are working to evaluate Flu-PRO patient-reported outcome instrument for COVID

Lisa LaVange to Everyone: 12:52 PM

We have visiting PhD students here today for a virtual campus visit, and I am in charge. See everyone next week. Great progress!

Libby Higgs to Everyone: **12:53 PM**

Next week we will do a more detailed presentation on ACTIV 3b focused on COVID-19 ARDS patients.

Timothy Buchman to Everyone: **12:54 PM**

@Libby, looking forward to it!

Walter Koroshetz to Everyone: **12:56 PM**

have to dig deeper but this report claimed outcome was time to feel well. https://www.clinicaltrialsarena.com/news/uk-study-azithromycin-doxycycline/?utm_source=Push%20Notification&utm_medium=website&utm_campaign=Push%20Notifications&utm_content=standard

Walter (b) (6) [redacted] to Everyone: **12:58 PM**

(b) (5) [redacted]

(b) (6) [redacted] **to Everyone:** **1:00 PM**

(b) (5) [redacted].

Libby Higgs to Everyone: **2:01 PM**

Agree will need a statistician and labatorian

Timothy Buchman to Everyone: **2:02 PM**

Thanks Stacey for keeping us on track!

High-Level Meeting Summary

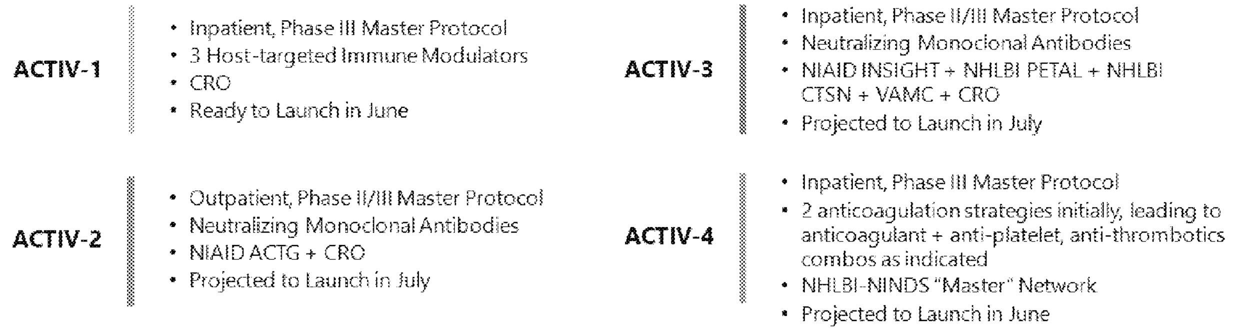
The Therapeutics-Clinical Working Group (TX-Clinical WG) heard updates from its Co-Chairs on yesterday's ACTIV Leadership Team call, and from its Master Protocol and Agent Prioritization Subgroups (MPSG and APSG, respectively). These updates addressed efforts to draft and plan for ACTIV master protocols, and to establish minimum gating criteria for considering SARS-CoV-2 monoclonal antibodies (mAbs) for ACTIV trials.

Leadership Team Call Update

During ACTIV's Leadership Team meeting yesterday, TX-Clinical WG Co-Chairs Drs. Eric Hughes and Sarah Read presented on the WG's progress and current efforts, including plans to design a master protocol to test mAb combinations and to conduct preclinical studies to accelerate the identification of promising mAb combinations. ACTIV Leadership discussed the WG's minimum entry criteria to consider an mAb (or mAb combination) for ACTIV testing, and some Leadership Team members expressed interest in attending the upcoming June 9 SARS-CoV-2 mAb Clinical Summit, which is being organized jointly by ACTIV and Operation Warp Speed.

Master Protocol Subgroup Updates

The MPSG presented on the designs of its various master protocols now under development:



ACTIV-1
- Inpatient, Phase III Master Protocol
- 3 Host-targeted Immune Modulators
- CRO
- Ready to Launch in June

ACTIV-2
- Outpatient, Phase II/III Master Protocol
- Neutralizing Monoclonal Antibodies
- NIAID ACTG + CRO
- Projected to Launch in July

ACTIV-3
- Inpatient, Phase II/III Master Protocol
- Neutralizing Monoclonal Antibodies
- NIAID INSIGHT + NHLBI PETAL + NHLBI CTSN + VAMC + CRO
- Projected to Launch in July

ACTIV-4
- Inpatient, Phase III Master Protocol
- 2 anticoagulation strategies initially, leading to anticoagulant + anti-platelet, anti-thrombotics combos as indicated
- NHLBI-NINDS "Master" Network
- Projected to Launch in June

The TX-Clinical WG may provide mAb expertise to augment ACTIV's prophylaxis efforts, which will likely be spearheaded by the Vaccines WG in coordination with NIAID's COVID Prevention Network.

ACTIV-1: Immunomodulators (Inpatient Phase III)

With input from Janssen, Bristol Myers Squibb, and AbbVie/Allergan, the ACTIV-1 writing team has completed an initial draft of its standalone master protocol and is hoping to locate a lead network by next week to support execution of the protocol. Discussions with NIAID, NHLBI, and NCATS networks are ongoing, but the team will also consider external networks with CRO support if necessary. In addition to its primary purpose of testing immunomodulators, ACTIV-1 will be capable of testing promising antivirals in phase III confirmatory trials should any such drugs become available. Earlier-stage antivirals could potentially be tested under ACTIV-2 or ACTIV-3.

ACTIV-2: Monoclonal Antibodies (Outpatient, Phase II/III)

ACTIV-2's Pre-IND was submitted to FDA on June 1, 2020, including a draft protocol and several queries for regulators. NIAID's Division of AIDS (DAIDS) is working closely with ACTG and PPD (a CRO) to delineate responsibilities for the trial and operationalize its implementation. Launch is tentatively targeted for the first week of July. Supply orders for non-study product items such as applicable swabs and diagnostics are now being placed, and DAIDS is working closely with Eli (b) [redacted] to ensure study product availability and distribution for the first study arm of the trial. Next steps are to receive and respond to FDA comments on the Pre-IND submission, to update the protocol as needed and submit the New IND to FDA, and to further solidify trial and data management logistics.

ACTIV-3: Monoclonal Antibodies (Inpatient, Phase II/III)

INSIGHT has been selected as the lead network for ACTIV-3 and will partner with the PETAL, CTSN, and VAMC networks. A synopsis outlining the study design has been developed to share with industry partners at the upcoming mAb Clinical Summit for their feedback. An initial outline of the master protocol will be developed by the end of this week for review by the mAb Steering Committee. The ACTIV-3 writing team is coordinating closely with the ACTIV-1 and -2 writing teams to harmonize protocols where needed. The ACTIV-3 operations team is planning its protocol implementation strategy and identifying collaboration opportunities across networks as well as additional needs for CRO support (like ACTIV-2, ACTIV-3 will enlist PPD for assistance).

ACTIV-4: Anticoagulants (Inpatient, Phase III)

The ACTIV-4 anticoagulant master protocol being led by NHLBI will initially apply two strategies for anticoagulation, which will then be adapted to combination strategies with both antiplatelet and antithrombotic agents. NHLBI has collaborated with NINDS, BARDA, and FDA to develop its master protocol, which is now under Data Safety Monitoring Board (DSMB) review. Enrollment is set to begin immediately upon DSMB approval.

Powering ACTIV Clinical Trials

Dr. (b)(6) [redacted] expressed (b)(5) [redacted]. Dr. (b)(6) [redacted] explained (b)(5) [redacted]. Dr. (b)(6) [redacted] (b)(5) [redacted]

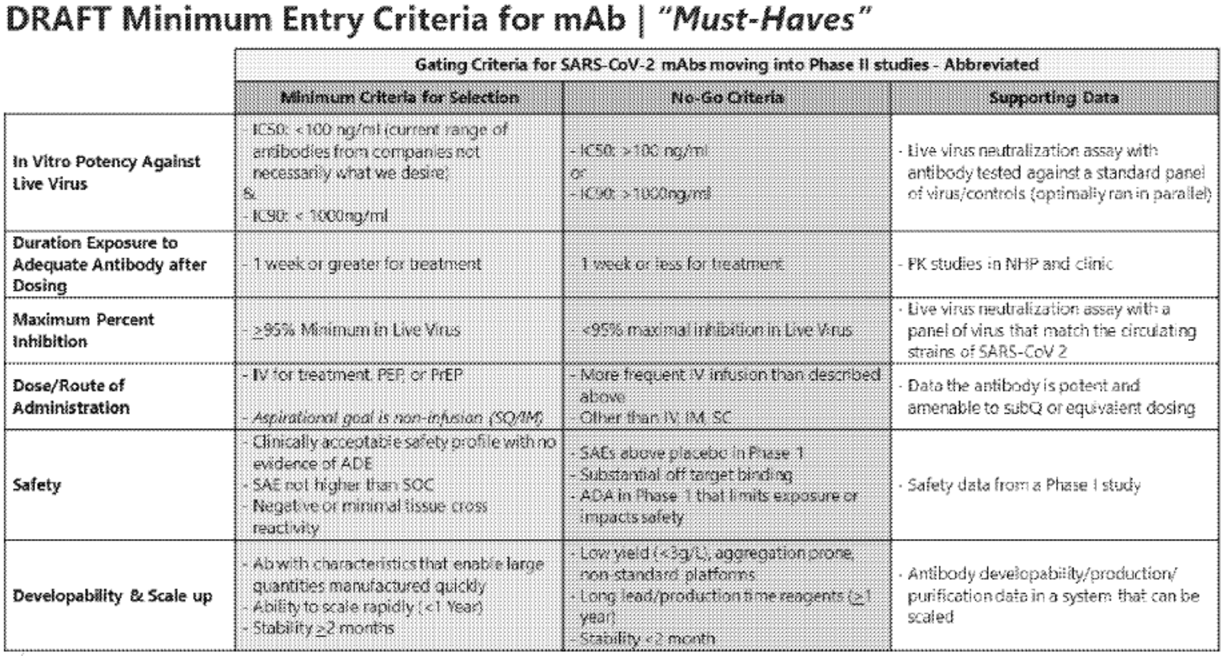
Dr. Adam will arrange for the Clinical Trial Capacity WG to present next week to the TX-Clinical WG on its clinical trial capacity and innovations inventory and dashboard. These tools will also help to ensure that ACTIV clinical trials are sufficiently powered to produce meaningful data.

Agent Prioritization Subgroup Updates

The APSG has broken into tactical subgroups, focusing mainly on establishing minimum entry criteria to consider mAbs for testing in ACTIV trials. The APSG has also met with Preclinical WG Co-Chairs to align prioritization efforts, and this week will finalize its web-based survey used to collect data on candidate agents.

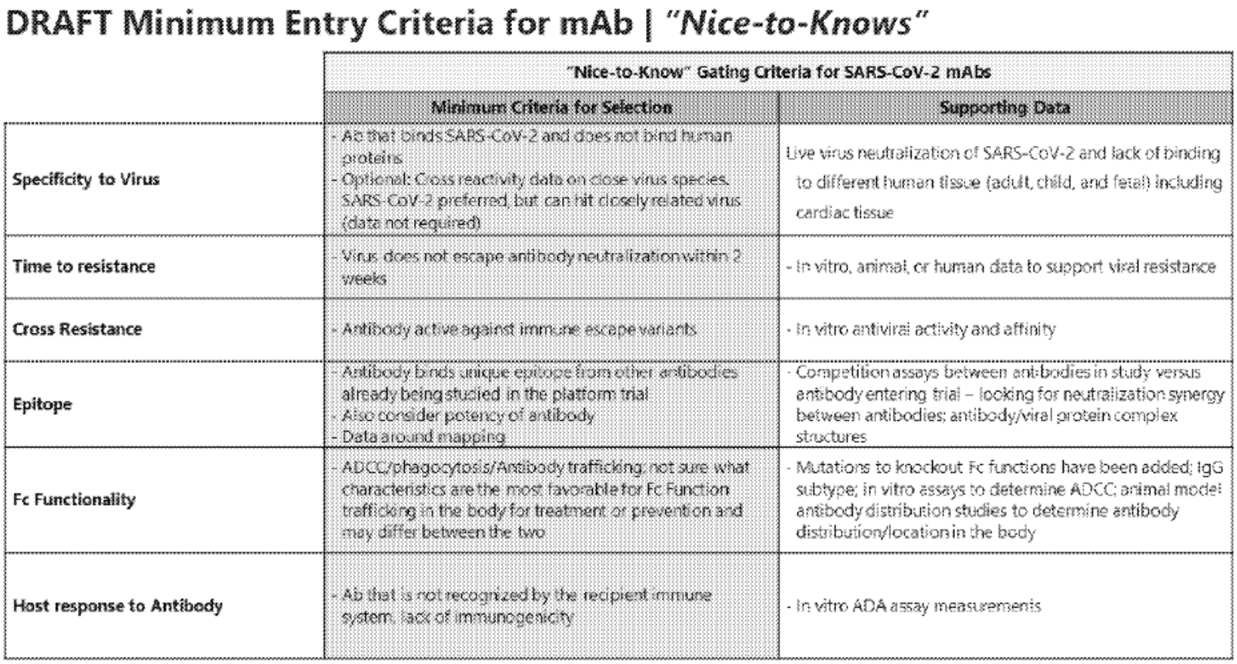
Monoclonal Antibody Subteam Update

After receiving feedback during last week's TX-Clinical WG meeting, the mAb Subteam revisited its minimum entry criteria for considering mAbs for ACTIV testing. These criteria are divided into "Must-Haves" with corresponding no-go criteria and "Nice-to-Knows." Dr. John Mellors, Chair of the mAb Subteam, presented its updated minimum entry criteria for mAbs, shown below:



DRAFT Minimum Entry Criteria for mAb | *"Must-Haves"*

	Gating Criteria for SARS-CoV-2 mAbs moving into Phase II studies - Abbreviated		
	Minimum Criteria for Selection	**No-Go Criteria**	**Supporting Data**
In Vitro Potency Against Live Virus	- IC50: <100 ng/ml (current range of antibodies from companies not necessarily what we desire) & - IC90: < 1000ng/ml	- IC50: >100 ng/ml or - IC90: >1000ng/ml	- Live virus neutralization assay with antibody tested against a standard panel of virus/controls (optimally ran in parallel)
Duration Exposure to Adequate Antibody after Dosing	- 1 week or greater for treatment	1 week or less for treatment	- PK studies in NHP and clinic
Maximum Percent Inhibition	- ≥95% Minimum in Live Virus	<95% maximal inhibition in Live Virus	- Live virus neutralization assay with a panel of virus that match the circulating strains of SARS-CoV 2
Dose/Route of Administration	- IV for treatment, PEP, or PrEP - *Aspirational goal is non-infusion (SQ/IM)*	- More frequent IV infusion than described above - Other than IV, IM, SC	- Data the antibody is potent and amenable to subQ or equivalent dosing
Safety	- Clinically acceptable safety profile with no evidence of ADE - SAE not higher than SOC - Negative or minimal tissue cross reactivity	- SAEs above placebo in Phase 1 - Substantial off target binding - ADA in Phase 1 that limits exposure or impacts safety	- Safety data from a Phase I study
Developability & Scale up	- Ab with characteristics that enable large quantities manufactured quickly - Ability to scale rapidly (<1 Year) - Stability ≥2 months	- Low yield (<3g/L), aggregation prone, non-standard platforms - Long lead/production time reagents (≥1 year) - Stability <2 month	- Antibody developability/production/ purification data in a system that can be scaled



DRAFT Minimum Entry Criteria for mAb | *"Nice-to-Knows"*

	"Nice-to-Know" Gating Criteria for SARS-CoV-2 mAbs	
	Minimum Criteria for Selection	**Supporting Data**
Specificity to Virus	- Ab that binds SARS-CoV-2 and does not bind human proteins - Optional: Cross reactivity data on close virus species. SARS-CoV-2 preferred, but can hit closely related virus (data not required)	Live virus neutralization of SARS-CoV-2 and lack of binding to different human tissue (adult, child, and fetal) including cardiac tissue
Time to resistance	- Virus does not escape antibody neutralization within 2 weeks	- In vitro, animal, or human data to support viral resistance
Cross Resistance	- Antibody active against immune escape variants	- In vitro antiviral activity and affinity
Epitope	- Antibody binds unique epitope from other antibodies already being studied in the platform trial - Also consider potency of antibody - Data around mapping	- Competition assays between antibodies in study versus antibody entering trial – looking for neutralization synergy between antibodies; antibody/viral protein complex structures
Fc Functionality	- ADCC/phagocytosis/Antibody trafficking: not sure what characteristics are the most favorable for Fc Function trafficking in the body for treatment or prevention and may differ between the two	- Mutations to knockout Fc functions have been added; IgG subtype; in vitro assays to determine ADCC; animal model antibody distribution studies to determine antibody distribution/location in the body
Host response to Antibody	- Ab that is not recognized by the recipient immune system, lack of immunogenicity	- In vitro ADA assay measurements

The mAb Subteam will remain active and has agreed to lead the evaluation of candidate mAbs.

Wave 2 Agent Prioritization

Wave 2 agent prioritization will begin soon across pre-established expert groups focused on antivirals, host-targeted immunomodulators, symptomatic/supportive therapies, and mAbs.

Next Steps

The ACTIV-2 writing team is awaiting FDA feedback on its Pre-IND submission, while the ACTIV-1 and ACTIV-3 writing teams continue to finalize their draft protocols. The MPSG subteams will continue to work with their partnering networks, agencies, companies, and CROs to plan for protocol implementation.

The APSG will collect potential investigative assets through its web-based survey (Dr. Adam will distribute a link to TX-Clinical WG members after this meeting), and will target outreach efforts to companies with the highest-priority agents, as well as to past submitters with requests that they use the survey to update their asset information.

Appendix A: Participants List

WORKING GROUP MEMBERS

Sam Bozzette, MD, PhD, *Chief Medical Officer, National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH)*

Timothy G. Buchman, MD, PhD, *Biomedical Advanced Research and Development Authority (BARDA)*

Timothy H. Burgess, MD, MPH, *Captain, Navy*

Joan Butterton, MD, *Associate VP, Clinical Research, Infectious Diseases, Merck & Co.*

Sylva Collins, PhD, *Director of the Office of Biostatistics, FDA*

Judith Currier, MD, *Professor of Medicine in the Division of Infectious Diseases, University of California, Los Angeles (UCLA)*

Angelo DeClaro, MD, *Division Director (Acting), Division of Hematologic Malignancies, Food and Drug Administration (FDA)*

Ruxandra Draghia-Akli, MD, PhD, *Global Head, Global Public Head R&D, Johnson & Johnson*

Mark Eisner, MD, MPH, *Senior VP, Global Head of Immunology, Infectious Disease, and Ophthalmology Clinical Development, Genentech*

Carl Garner, PhD, *VP, Global Regulatory Affairs, Eli Lilly*

Elizabeth (Libby) Higgs, MD, MIA, DTM&H, *Global Health Science Advisor, National Institute of Allergy and Infectious Diseases (NIAID)*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis (WG Co-chair)*

Walter Koroshetz, MD, *Director, National Institute of Neurological Diseases and Stroke (NINDS)*

Lisa LaVange, PhD, *Associate Chair, Department of Biostatistics, UNC*

John Mellors, MD, *Professor of Medicine, Chief of Infectious Diseases Division, U. Pittsburgh*

Naimish Patel, MD, *Global Development Head of Therapeutic Area, Immunology and Inflammation, Sanofi*

Amanda Peppercorn, MD, *Senior Medical Director, Infectious Disease, GlaxoSmithKline (GSK)*

Michael Proschan, PhD, *Mathematical Statistician, Biostatistics Research Branch, NIAID, NIH*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH (WG Co-chair)*

Daniel Ruben, PhD, *Division of Biometrics IV, CDER, FDA*

Peter Stein, MD, *Director of Office of New Drugs, CDER, FDA*

INVITED PARTICIPANTS

Christine Colvis, PhD, *Director for Drug Development Partnership Programs, NCATS, NIH*

Michelle Culp, MPH, *Office of the Director, NIH*

Ellen Gadbois, PhD, *Office of Science Policy, Office of the Director, NIH*

W. Keith Hoots, MD, *Director, Division of Blood Diseases and Resources, NHLBI*

Jacqueline Kirchner, PhD, *Senior Program Officer, Discovery and Translational Sciences*

Hilary D. Marston, MD, MPH, *Medical Officer/Policy Advisor, NIAID, NIH*

Ashley Parker, PhD, *Health Science Policy Analyst, NIH*
Dionne Price, PhD, *Director, Division of Biometrics IV, CDER, FDA*
Felicia Qashu, PhD, *Program Officer, NIH*
Lora Reineck, MD, *Program Director, Lung Biology and Disease Branch, NHLBI*
Yves Rosenberg, MD, MPH, *Atherothrombosis and Coronary Artery Disease Branch Chief, NHLBI*
Peter Wung, MD, MPH*, Associate VP, Global OMD Lead, Immuno-Inflammation, Sanofi*
John Young, PhD, *Global Head, Infectious Diseases, Roche*

STAFF
Stacey Adam, PhD, *Scientific Program Manager for Cancer, Foundation for the NIH (FNIH)*
Karen Tountas, PhD, *Scientific Program Manager, FNIH*
David Wholley, MPhil, *Senior VP of Research Partnerships, FNIH*

Rosa Maria Alvarez, PhD*, Consultant, Deloitte*
Helen Q. Chen, PhD, *Senior Consultant, Deloitte*
Benjamin Stratton, PhD, *Senior Consultant, Deloitte*
Jonathan Wachtel*, Manager, Deloitte*

Lucas Smalldon, MA, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

Timothy Buchman: 16:12

(b) (5) [redacted]. Is there work being done to model the potential numbers of enrollable subjects? Are there strategies to ensure the highest probability of getting to a meaningful result even in low enrollment?

TimBurgess: 16:36

That is a great question

walter Koroshetz: 17:13

send link for summit next week?

Mark Eisner: 21:24

How is ACTT enrolling?

Mark Eisner: 21:31

ACTT2 that is

Mark Eisner: 25:34

Thank you

Sarah Read: 25:46

ACTT2 has (b) (4) [redacted] so far (b) (4) [redacted])...slower enrollment than ACTT1

Michael Proschan: 30:08

It looks like ACTT2 has reached (b) (4) [redacted]

Timothy Buchman: 30:29

Nice to hear--thanks!

Judith Currier: 32:29

I need to drop off- not sure if you could hear me, but ACTIV-2 team remains interested in arms for small molecules

Joan Butterton: 33:02

Thanks, as all know I am strongly supportive of this

(b) (6) [redacted] **49:40**

What are the initial arms in ACTIV-4?

Timothy Buchman: 50:14

I too am especially interested in those initial arms and how they interface with current standard-of-care.

(b) (6) 50:25

arms=strategies

Timothy Buchman: 51:37

The equipoise question is key.

Action Items

Action	Owner
1. Set metrics related to cycle times and benchmarks for improvement in order to accelerate the preclinical space	Preclinical Working Group
2. Share the Preclinical and Therapeutics Clinical survey link with HEVER and the R&D Consortium to broaden the reach of respondents	Preclinical and Therapeutics Clinical Working Groups
3. Establish benchmark of preclinical assessment (including assays, graduating criteria, etc.) for mAb combinations and cocktails and if possible, receive input by the June 9th Summit	Preclinical and Therapeutics Clinical Working Groups

Meeting Summary

The Leadership Team overseeing the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) Partnership convened to review progress made since May 6, 2020. Drs. Francis Collins and Paul Stoffels, Co-Chairs of the ACTIV Leadership Team, opened the meeting by outlining the relationship between ACTIV, Operation Warp Speed (OWS), and industry partners. Following their overview, the Leadership Team received updates from Co-Chairs of all four ACTIV Working Groups (WGs), which cover the following focus areas: (1) Preclinical; (2) Therapeutics Clinical (TX-Clinical); (3) Clinical Trial Capacity (CTC); and (4) Vaccines. The Leadership Team discussed progress made by each WG so far and consulted the WG Co-Chairs about their ongoing activities and further action plans.

Introduction

Francis Collins, PhD, MD, Director, NIH; Paul Stoffels, MD, Vice Chairman of the Executive Committee and Chief Scientific Officer, Johnson & Johnson

Dr. Collins provided more information about the relationship between ACTIV's Public-Private Partnership and OWS, the overarching initiative through which the federal government seeks to coordinate all processes and resources to ensure the fastest possible action against COVID-19. Led by Dr. Moncef Slaoui with support from General Gustave F. Perna, OWS is working to ensure that all diagnostic, therapeutic, and vaccine efforts seamlessly coordinate, and that emergency Congressional funding supports activities with the best chance to save lives. OWS draws on subject matter experts from multiple agencies, reflecting its coordinating mission: it is co-chaired by Secretaries of the Department of Health and Human Services and Department of Defense, and its three work streams are overseen as follows: **Diagnostics**—Dr. Bruce J. Tromberg, PhD, Director of the National Institute of Biomedical Imaging and Bioengineering (NIBIB); **Therapeutics**—Dr. Janet Woodcock (who has stepped away from FDA to focus entirely on this effort); and **Vaccines**—Colonel Matthew Hepburn, MD, Joint Project Lead, US Army.

ACTIV's efforts are making a critical contribution to OWS by defining potential preclinical, therapeutic, and vaccine priorities and by building the necessary components of implementation plans, such as master protocols and inventories of clinical trial capacity. These contributions help OWS to assign resources effectively and ensure strong outcomes.

Dr. Paul Stoffels noted that federal activities are complemented by equally important industry efforts to expand manufacturing capacity for vaccines and therapeutics. He shared an update from the June 2 meeting of the HEVER Group, which annually brings together representatives of industry, regulatory, and public health agencies in the United States and Europe to accelerate science for the world's benefit. This year's meeting included a discussion of principles of data sharing that are particularly relevant to COVID-19 initiatives. All public and private institutions are working with the shared purpose of bringing COVID-19 quickly under control.

Therapeutics-Preclinical WG

Christine Colvis, PhD, National Center for Advancing Translational Sciences (NCATS); John Young, PhD, Roche

The Preclinical WG reviewed its progress on the five components of its mandate: (1) it has completed a master inventory of preclinical testing resources; (2) it has developed a national strategy for non-human primate (NHP) resources that is under review by National Primate Research Center directors; and (3) it is building a virtual in vitro and in vivo preclinical testing network. The bulk of the WG's most recent work has focused on (4) developing a compound prioritization plan and (5) building a public database for comprehensive data sharing.

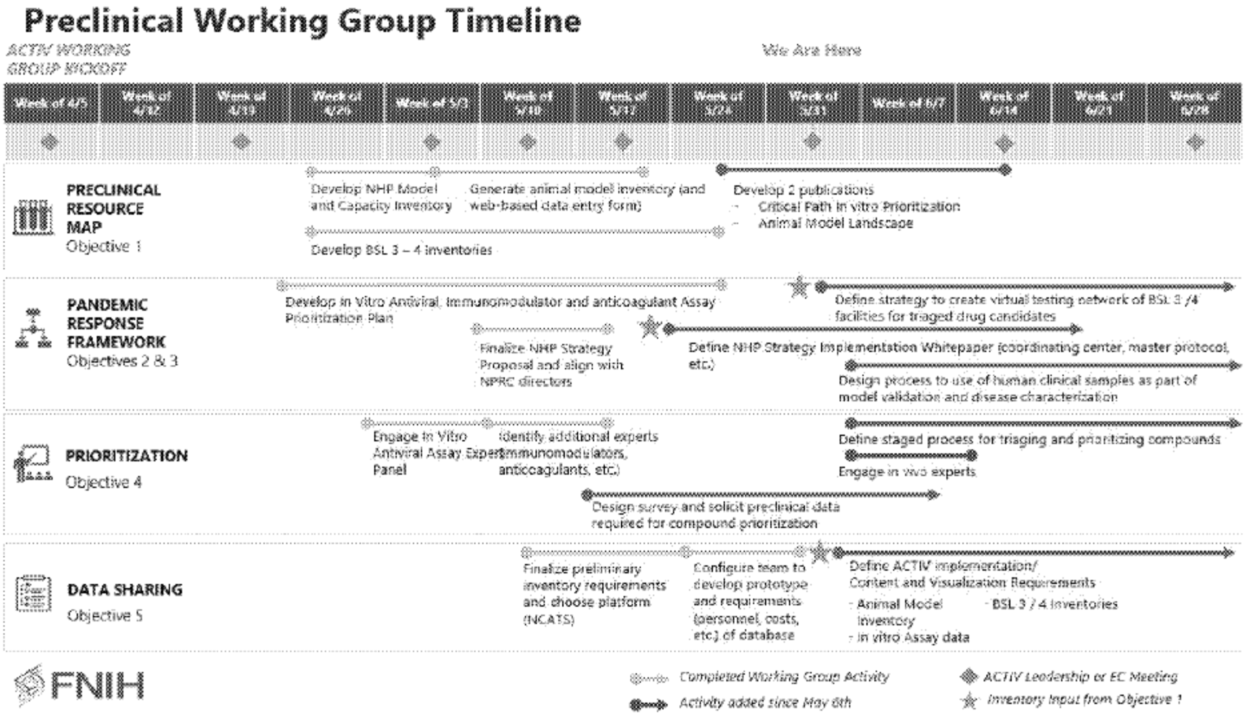
Prioritization Plan

The WG is finalizing a web-based survey—developed with input from this WG as well as the TX-Clinical and Vaccines WG—to collect data that will help facilitate compound prioritization. The survey will be sent to compound sponsors on June 8 to collect data for the next round of agent prioritization. The Leadership Team can support this effort by encouraging colleagues and contacts to respond to the survey and thus help identify promising agents that can be prioritized for ongoing clinical trials. Collected data will remain confidential and available only to ACTIV members and prioritization panel reviewers.

Preclinical prioritization criteria have been designed to support a "pandemic response mode" that advances drugs rapidly into the clinical setting. The WG has identified a set of accelerated preclinical screening funnels for all agent classes of interest, including antivirals, immunomodulators, anticoagulants, complement modulators, and other agents (repurposed drugs may require even less preclinical testing). Non-gating studies that are required in typical testing processes will instead be conducted in parallel with clinical trials.

Public Database

The animal model data collected by the WG (on 45 small animal and 25 NHP models) will be shared in the NCATS portal, which is now live and updated regularly. Data visualizations to facilitate the portal's use are being developed. The database will help users identify and fill critical gaps in information needed to validate models; those gaps related to African green monkeys and rhesus monkeys will be addressed by work in ACTIV, while external research will address small animal systems. The WG also recognizes the importance of reverse-translating emerging human clinical data into the design of animal studies and is conducting ongoing discussions with other WGs about how best to achieve that goal.



Preclinical Working Group Timeline

ACTIV WORKING GROUP KICKOFF

We Are Here

Week of 4/5 | Week of 4/12 | Week of 4/19 | Week of 4/26 | Week of 5/3 | Week of 5/10 | Week of 5/17 | Week of 5/24 | Week of 5/31 | Week of 6/7 | Week of 6/14 | Week of 6/21 | Week of 6/28

PRECLINICAL RESOURCE MAP
Objective 1

Develop NHP Model and Capacity Inventory

Generate animal model inventory (and web-based data entry form)

Develop BSL 3 – 4 inventories

Develop 2 publications
- Critical Path in vitro Prioritization
- Animal Model Landscape

PANDEMIC RESPONSE FRAMEWORK
Objectives 2 & 3

Develop in Vitro Antiviral, Immunomodulator and anticoagulant Assay Prioritization Plan

Finalize NHP Strategy Proposal and align with NPRC directors

Define strategy to create virtual testing network of BSL 3 /4 facilities for triaged drug candidates

Define NHP Strategy Implementation Whitepaper (coordinating center, master protocol, etc.)

Design process to use of human clinical samples as part of model validation and disease characterization

PRIORITIZATION
Objective 4

Engage in Vitro Antiviral Assay Expert Panel

Identify additional experts (immunomodulators, anticoagulants, etc.)

Design survey and solicit preclinical data required for compound prioritization

Define staged process for triaging and prioritizing compounds

Engage in vivo experts

DATA SHARING
Objective 5

Finalize preliminary inventory requirements and choose platform (NCATS)

Configure team to develop prototype and requirements (personnel, costs, etc.) of database

Define ACTIV implementation/ Content and Visualization Requirements
- Animal Model Inventory
- In vitro Assay data
- BSL 3 / 4 Inventories

FNIH

Completed Working Group Activity

Activity added since May 6th

ACTIV Leadership or EC Meeting

Inventory input from Objective 1

Discussion

Following their presentation, the WG Co-Chairs answered Leadership Team questions.

Survey Recipients

The WG plans to circulate its web-based survey to three groups: (1) sponsors of compounds prioritized by the Preclinical and TX-Clinical WGs, (2) sponsors that submitted compound data via the NIH COVID-19 website; and (3) asset-holders identified by the ACTIV Executive Committee. At Dr. William Pao's recommendation, the WG will also send the survey link to the Hever Group and COVID R&D Consortium to broaden respondent reach.

Preclinical Testing Capacity

The WG is establishing parameters to help companies structure preclinical studies and understand the kinds of assays required to make compounds eligible for clinical prioritization. However, studies will be conducted by sponsors, and thus those sponsors will determine the precise number of compounds that use these resources. The WG will collaborate with the virtual network it is building to coordinate tests for specific agents prioritized by ACTIV.

Metrics to Accelerate Progress

The WG has established some metrics for assessing preclinical trials, primarily related to potency of molecules. It will set metrics for cycle times and benchmarks of improvement in order to accelerate work in the preclinical space.

Therapeutics-Clinical WG

Eric Hughes, MD, PhD, Novartis; Sarah Read, MD, NIAID

The TX-Clinical WG has made significant progress on its two-part mandate: (1) to prioritize therapeutic agents for testing against COVID-19 and (2) to develop an adaptive master protocol strategy to be quickly launched in trial networks.

Agent Prioritization

Since completing Agent Prioritization Wave 1 (which identified three immunomodulators and several anticoagulants for immediate clinical testing), the WG has updated the prioritization process for Wave 2 to include refined scoring criteria for antivirals and immunomodulators and an expanded process for collecting supporting data. The new data collection process will synthesize publicly available data, a web-based Request for Information, and submissions from investigators.

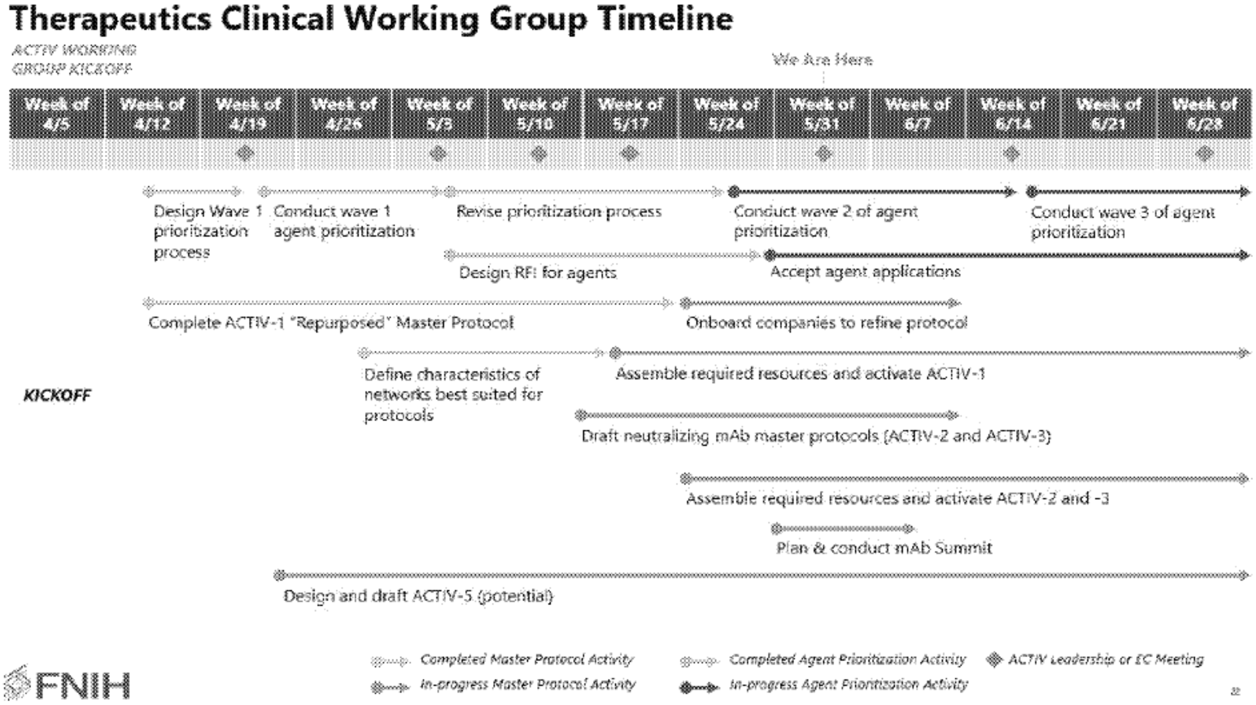
The WG has also developed a new process to bring monoclonal antibodies (mAbs) into ACTIV clinical trials. The WG has established minimum criteria and "nice-to-have" data to assess potential mAbs for inclusion (minimum criteria include potency against live virus, duration of exposure for dosing, max percent inhibition, dose/route of administration, safety, developability and scalability). A June 9 summit will bring together ACTIV and mAb developers to introduce these criteria and identify agents that can be enrolled in a first round of trials.

Master Protocols

The WG has made rapid progress on a large number of master protocols:

- ACTIV-1—to test immunomodulators identified in Wave 1—is nearly complete, with three company sponsors currently adjusting agent-specific monitoring criteria.
- ACTIV-2—to test mAbs in outpatients—has been submitted to FDA for pre-IND review; ACTG has been selected as the lead network, with the potential for additional trial sites and support from a contract research organization (CRO).
- ACTIV-3—to test mAbs in inpatients—is being drafted in collaboration with the INSIGHT, PETAL, and CTSN networks; eventual trial support from Veterans Affairs (VA) and a CRO is also likely.
- ACTIV-4—to test anticoagulants—is being drafted in collaboration with NHLBI and NINDS.

The WG will assess whether an additional ACTIV-5—to take in agents appropriate for Phase II evaluation—is necessary. ACTIV-2 and -3 are both agnostic to agent type (specific agents are addressed by appendices) and thus could serve as platforms for non-mAb interventions, which would obviate the need for an ACTIV-5.


Therapeutics Clinical Working Group Timeline
ACTIV WORKING GROUP KICKOFF
We Are Here
Week of 4/5
Week of 4/12
Week of 4/19
Week of 4/26
Week of 5/3
Week of 5/10
Week of 5/17
Week of 5/24
Week of 5/31
Week of 6/7
Week of 6/14
Week of 6/21
Week of 6/28
Design Wave 1 prioritization process
Conduct wave 1 agent prioritization
Revise prioritization process
Conduct wave 2 of agent prioritization
Conduct wave 3 of agent prioritization
Design RFI for agents
Accept agent applications
Complete ACTIV-1 "Repurposed" Master Protocol
Onboard companies to refine protocol
Define characteristics of networks best suited for protocols
Assemble required resources and activate ACTIV-1
KICKOFF
Draft neutralizing mAb master protocols (ACTIV-2 and ACTIV-3)
Assemble required resources and activate ACTIV-2 and -3
Plan & conduct mAb Summit
Design and draft ACTIV-5 (potential)
Completed Master Protocol Activity
In-progress Master Protocol Activity
Completed Agent Prioritization Activity
In-progress Agent Prioritization Activity
ACTIV Leadership or EC Meeting
FNIH
22

Discussion

Following their presentation, the WG Co-Chairs responded to Leadership Team questions and discussion points.

Single versus Combination Antibodies

The WG intends to begin mAb tests with single antibodies and subsequently test drug combinations in new study arms, which can be rapidly added under both ACTIV-2 and -3. Developers who already have sufficient combination data to justify Phase II trials can be immediately considered. However, while the ACTIV master protocols and FDA regulations both allow antibody combinations to enter clinical trials, manufacturing readiness is likely to pose a more significant obstacle. A single antibody that can be quickly manufactured can have greater practical effectiveness than a slightly more potent combination whose multiple components cannot be quickly sourced.

Preclinical Strategy to Assess Antibody Combinations

Participants discussed the possibility of developing a preclinical strategy to shed light on potential antibody combinations in parallel with the initial clinical focus on single antibodies. This parallel approach could help ensure that no promising agent falls behind ACTIV's urgent timeline. The UK has developed such an effort, which examines all antibodies developed by all biotechnology firms in synergy assays to ascertain the best possible combinations. ACTIV could form a similar effort by synthesizing existing data accessible from its industry partners or by catalyzing industry data collection. One potential preclinical data point that ACTIV could consider would be time to resistance. Dr. Collins directed the Preclinical and TX-Clinical WGs to develop an initial benchmark of preclinical assessment (including assays and graduating criteria) before the June 9 mAb summit for feedback before or during that gathering.

June 9 Summit

Dr. Woodcock clarified that all ACTIV members are welcome to attend the June 9 mAb summit. Master protocol synopses will also be available for review before the event takes place.

Clinical Trial Capacity WG

Elizabeth Desrosiers, MS, PMP, Merck; Michael Kurilla, MD, PhD, NCATS

The CTC WG has made significant progress on the three elements of its mandate: (1) it has developed an inventory of clinical trial capacity networks, sites, CROs, and site management organizations (SMOs); (2) it has analyzed the resulting data to enable the most efficient deployment of trial resources; and (3) it has identified innovations to enhance trial efficiency.

Inventory of Clinical Trial Capacity

The survey developed by the WG has collected responses from 52 networks, 586 sites, and 34 CROs/SMOs. Having initially focused on "shovel-ready" networks that could launch clinical trials in less than six weeks, the WG is now seeking specialty networks (e.g., pediatric networks) that may be important in vaccine trials.

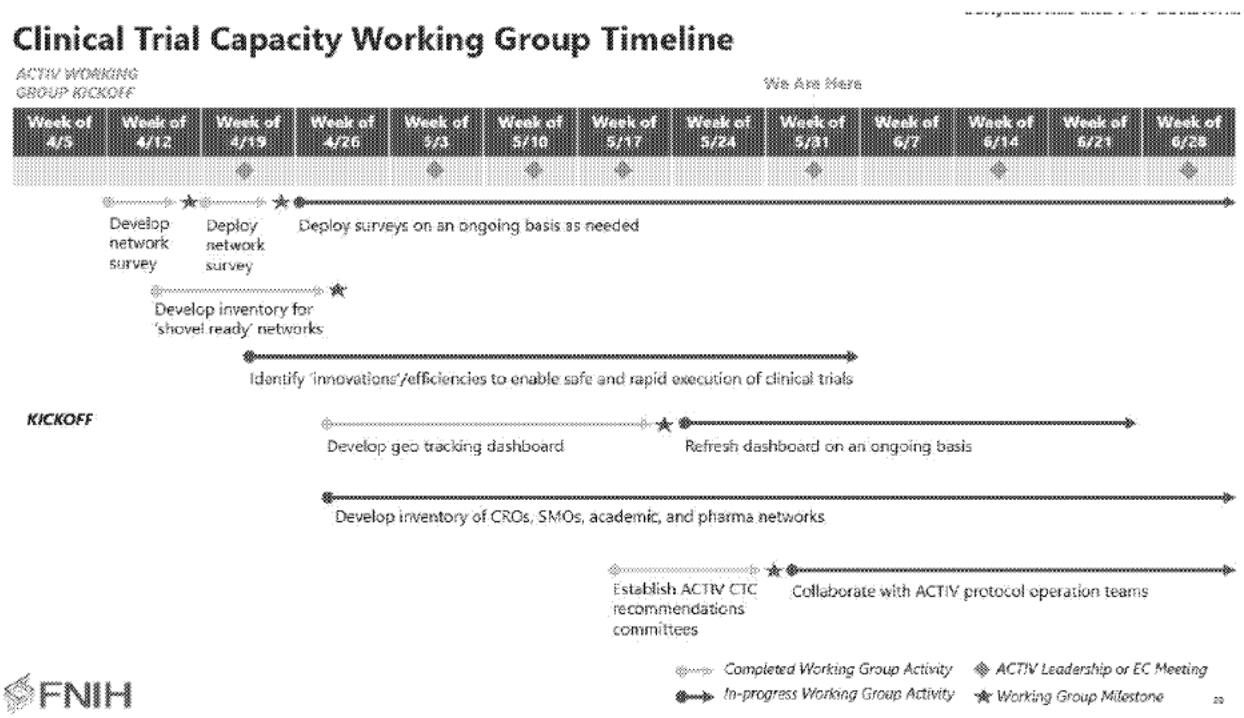
Analysis of Inventory Data

The data collected by the WG has been turned into a geo-tracking dashboard that supports quick and nuanced analysis of clinical trial capacity. A video demonstration of the dashboard showed that it presents color-coded sites that can be filtered through drop-down menus by network, location (from the world to county levels), time to readiness, and ability to execute master protocols. This information can be overlaid with rolling county-level case data from Johns Hopkins University and predictive data from Penn Medicine's CHIME tool.

The WG has developed a new process to ensure it can quickly use its analytic tools to respond to requests from the TX-Clinical and Vaccines WGs for recommendations of networks, sites, and CROs/SMOs. The process focuses on tiger teams of two to three people; one team has been established for inpatient trials (ACTIV-1 and -3) and another for outpatient trials (ACTIV-2).

Innovations

The WG has focused on identifying innovations that enable low-touch data collection throughout the entire clinical trial process. It is currently identifying home nursing services that may be critical to executing outpatient studies in ACTIV-2.



Clinical Trial Capacity Working Group Timeline

Discussion of Global Sites

Following their presentation, the WG Co-Chairs responded to Leadership Team questions regarding the global scope of its inventory. The WG inventoried global networks and sites and probed the ability of CROs/SMOs to orchestrate a global study. However, which sites are employed in particular trials will be determined by the Therapeutics-Clinical and Vaccine WGs and the networks themselves. Participants noted that vaccine trials will likely require a global network to ensure adequate enrollment and are aware that a vaccine must be distributed in any country where it is tested.

Vaccines WG

Kathrin Jansen, PhD, Pfizer; Douglas Lowy, MD, National Cancer Institute (NCI)

The Vaccines WG has made progress on all three aspects of its mandate: (1) it has aligned on a harmonized efficacy trials approach; (2) it has refined understanding of data requirements for more rapid approval or authorizations; and (3) it has developed two manuscripts to address cross-cutting vaccine development questions.

Harmonized Master Protocol for Vaccine Evaluation

The WG has developed a harmonized vaccine trials framework. The framework defines potential endpoints (related to symptomatic disease, infection, and moderate or severe disease); populations to be studied (adult ages with a low percentage of seropositives); and success criteria and sample size (efficacy of at least 50 percent with a lower bound of at least 20 percent at 90 percent power; trial sized to reach endpoint goal within six months; and monitoring for success or futility). While the harmonized protocol will be used for vaccines tested under government sponsorship, other manufacturers may elect to conduct trials independently with the same parameters. The WG recommends FDA-level harmonization to ensure comparable outputs across all studies.

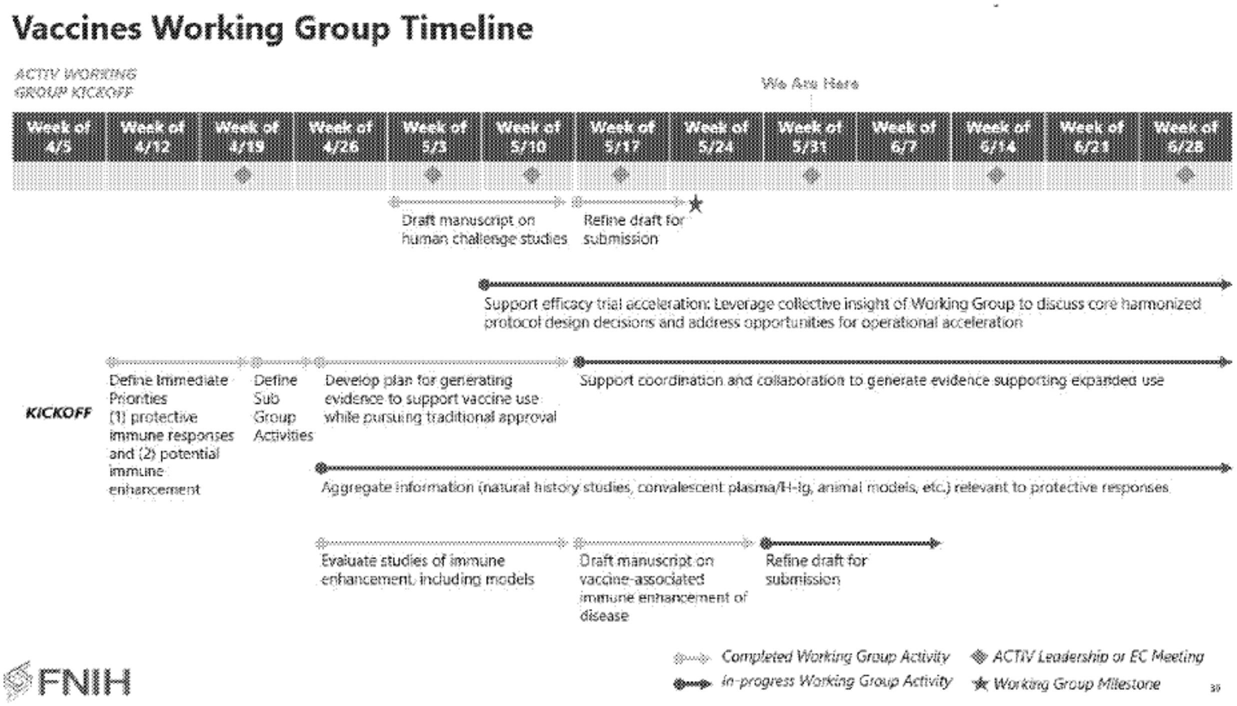
The WG will next consider which sites have the capacity to conduct trials within its framework. In addition to drawing on information collected by the CTC WG, it will likely use a CDC tool that currently can forecast incidence 4 weeks in advance nationally, but with limited ability to predict hot spots. This tool can help maximize enrollment in areas with high incidence, especially as the CDC works to improve forecasting at the county level.

Complementary Regulatory Pathways

The WG has created a table of requirements for accelerated introduction of vaccines before final efficacy data are available. The table (accessible as an appendix to the slide deck for this meeting) identifies requirements for treatment INDs, Emergency Use Authorization, and Accelerated Approval. The table will be supplemented with requirements for accelerated use of vaccines in Europe.

Manuscript Development

The WG has submitted a manuscript on the scientific and practical reasons that a controlled human infection model is unlikely to accelerate COVID-19 vaccine development. It also identified three issues that could be addressed in a human infection model that appropriately balanced benefits, risks, and mitigations: (1) correlates of protection, (2) durability of protection, and (3) immunopathogenesis. The WG is developing a second manuscript regarding vaccine-associated immune enhancement.



Vaccines Working Group Timeline

ACTIV WORKING GROUP KICKOFF

We Are Here

Week of 4/5	Week of 4/12	Week of 4/19	Week of 4/26	Week of 5/3	Week of 5/10	Week of 5/17	Week of 5/24	Week of 5/31	Week of 6/7	Week of 6/14	Week of 6/21	Week of 6/28
		◆		◆	◆	◆		◆		◆		◆

Draft manuscript on human challenge studies

Refine draft for submission ★

Support efficacy trial acceleration: Leverage collective insight of Working Group to discuss core harmonized protocol design decisions and address opportunities for operational acceleration

KICKOFF

Define Immediate Priorities (1) protective immune responses and (2) potential immune enhancement

Define Sub Group Activities

Develop plan for generating evidence to support vaccine use while pursuing traditional approval

Support coordination and collaboration to generate evidence supporting expanded use

Aggregate information (natural history studies, convalescent plasma/H-Ig, animal models, etc.) relevant to protective responses

Evaluate studies of immune enhancement, including models

Draft manuscript on vaccine-associated immune enhancement of disease

Refine draft for submission

Completed Working Group Activity

In-progress Working Group Activity

◆ *ACTIV Leadership or EC Meeting*

★ *Working Group Milestone*

Discussion

Following their presentation, the WG Co-Chairs responded to Leadership Team questions and discussion points.

Efficacy Data

Dr. Anthony Fauci noted that accelerated approvals can sometimes undermine the collection of data in randomized controlled clinical trials, which are necessary to demonstrate vaccine efficacy. The WG expects that Phase III efficacy studies will begin well before any vaccine would be considered for a complementary regulatory pathway; moreover, it expects that those studies can be completed on an expedited timeline that would make complementary pathways irrelevant. Only a delay in efficacy trials *combined with* availability of a vaccine candidate and evidence of likely effectiveness would lead to revisiting such pathways. Participants agreed on the importance of efficacy trials and noted that regulatory frameworks in the United States and Europe would prioritize their completion. They also noted that those trials will continue in sub-populations even after an effective vaccine is identified. Dr. Dolsten suggested that preclinical testing also has a key role to play in generating data that can identify surrogates of outcomes.

Data Standardization

Dr. Skip Virgin emphasized the importance of banking samples and harmonizing assays across different trial efforts to ensure effective assessment of trial outcomes, particularly in the context of analysis of correlates of protection. The WG noted that its harmonized framework will ensure comparability for antibody responses and banking of samples. Companies undertaking independent trials could participate directly or indirectly in such comparable studies.

Overall Leadership Team Feedback

Dr. Collins invited members of the Leadership Team to send additional feedback on WG activities to David Wholley, who will forward them to the Executive Committee (EC). The EC will meet every other week (its next meeting is June 17), and the Leadership Team will meet monthly (its next meeting is July 1). As ACTIV continues to make unprecedented progress, these meetings will continuously reassess expectations, plans, and new considerations/opportunities.

Appendix A: Participants List

Francis Collins, MD, PhD, *Director, National Institutes of Health (NIH) (Session Leader)*

Christopher P. Austin, MD, *Director, NCATS, NIH*

Marco Cavaleri, PhD, *Head of Biological Health Threats and Vaccines Strategy, EMA*

Tomas Cihlar, PhD, *VP of Virology, Gilead Sciences*

Christine Colvis, PhD, *Director for Drug Development Partnership Programs, National Center for Advancing Translational Sciences (NCATS), NIH*

Larry Corey, MD, *President and Director Emeritus, Fred Hutchison Cancer Research Center*

Gary Disbrow, PhD, *Director, Division of CBRN Countermeasures, HHS and Acting Director, BARDA*

Elizabeth Desrosiers, MS, PMP, *Executive Director, Clinical Sciences and Study Management, Merck*

Mikael Dolsten, MD, PhD, *CSO and President, Worldwide R & D, Pfizer*

Emily Erbelding, MD, MPH, *Director, Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases (NIAID), NIH*

Anthony Fauci, MD, *Director, NIAID, NIH*

Maria Freire, PhD, *President and Executive Director, FNIH*

Ellen Gadbois, PhD, *Program Lead, Emerging Biotechnology Policy, NIH Office of Science Policy*

Jordan Gladman, PhD, *Health Program Specialist, NIH*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis*

Kathrin Jansen, PhD, *Senior Vice President, Head of Vaccine Research and Development, Pfizer*

Michael Kurilla, MD, PhD, *Director, Division of Clinical Innovation, NCATS, NIH*

H. Clifford Lane, MD, *Deputy Director for Clinical Research and Special Projects, NIAID*

Douglas Lowy, MD, *Principal Deputy Director, National Cancer Institute (NCI), NIH*

Peter Marks, PhD, *Director, Center for Biologics Evaluation and Research, FDA*

Hilary D. Marston, MD, MPH, *Medical Officer/Policy Advisor, NIAID, NIH*

John Mascola, MD, *Director, Vaccine Research Center, NIAID, NIH*

David Meeker, MD, *KSQ Therapeutics (formerly Genzyme)*

Nancy Messonnier, MD, *Director, National Center for Immunization and Respiratory Diseases (NCIRD), CDC*

Mene Pangalos, PhD, *EVP, BioPharmaceuticals R&D, AstraZeneca*

William Pao, PhD, MD, *Head, Pharma Research & Early Development, Roche/Genentech*

Ashley Parker, PhD, *Health Science Policy Analyst, NIH*

Robert M. Plenge, MD, PhD, *SVP, Research & Early Development and Head, Immunology, Cardiovascular, Fibrosis, and Global Health Thematic Research Center, Bristol-Myers Squibb*

Andrew S. Plump, MD, PhD, *President, Research and Development, Takeda*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH*
Doris J. Rouse, PhD, *VP, Global Health Technologies, RTI International*
Daniel M. Skovronsky, MD, PhD, *Senior Vice President and Chief Scientific Officer, Eli Lilly and Co.*
Peter Stein, MD, *Director, Office of New Drugs, FDA*
Paul Stoffels, MD, *Vice Chairman of the Executive Committee and Chief Scientific Officer, Johnson & Johnson*
Lawrence Tabak, DDS, PhD, *Principal Deputy Director, NIH*
John Tsai, MD, *Head, Global Drug Development and CMO, Novartis*
Herbert (Skip) Virgin, MD, PhD, *EVP Research and CSO, Vir Biotechnology*
Janet Woodcock, MD, *Director, Center for Drug Evaluation and Research (CDER), FDA*
John Young, PhD, *Global Head, Infectious Diseases, Roche*

John T. Burklow, *Associate Director for Communications and Public Liaison, NIH*
Gary H. Gibbons, MD, *Director, NHLBI, NIH*
Adrienne Hallett, *Associate Director for Legislative Policy and Analysis, NIH*
Carrie D. Wolinetz, PhD, *Associate Director for Science Policy, NIH*

Stacey Adam, PhD, *Director, Foundation for the NIH (FNIH)*
Abbey Meltzer, MPS, *Vice President of Communications and Events, FNIH*
Joseph P. Menetski, PhD, *Associate VP of Research Partnerships, FNIH*
Michael Santos, PhD, *Associate VP of Science, FNIH*
Karen Tountas, PhD, *Scientific Program Manager, FNIH*
David Wholley, MPhil, *Senior VP of Research Partnerships, FNIH*

Margaret Anderson, *Managing Director, Deloitte*
Nina Gonzalez, *Senior Manager, Deloitte*
Benjamin Stratton, *Manager, Deloitte*
Jonathan Wachtel, *Manager, Deloitte*
Brett Tolman, *Strategy Consultant, Deloitte*
Rosa Alvarez, *Senior Consultant, Deloitte*
Helen Chen, *Senior Consultant, Deloitte*
Olivia Elsaid, *Consultant, Deloitte*

Dana Carluccio, PhD, *Writer, Rose Li and Associates, Inc.*

Questions & Comments: *All questions and comments from this meeting have been incorporated into this summary document.*

High-Level Meeting Summary

The Clinical Trial Capacity Working Group (CTC WG), co-chaired by Elizabeth Desrosiers and Michael Kurilla, convened to learn about the Rapid Acceleration of Diagnostics (RADx) Initiative and to receive updates about WG activity.

RADx will leverage the NIH Point-of-Care Technology Research Network (POCTRN) to accelerate the development, validation, and commercialization of innovative point-of-care and home-based tests that can detect SARS-CoV-2. The program is structured to provide escalating support to awardees in a four-phase gated manner, ending in large-scale manufacturing and distribution of viable tests. Its goal is to deploy millions of tests per week by fall 2020.

Below is a summary of the key discussion themes.

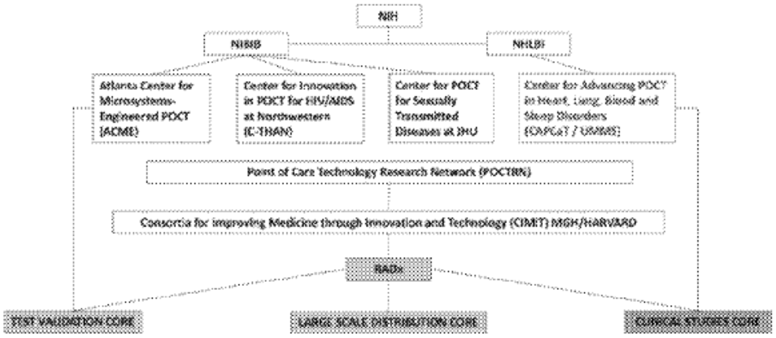
Rapid Acceleration of Diagnostics

RADx representatives presented on the initiative's mission, organization, process, and protocols. Supported by the National Institute of Biomedical Imaging and Bioengineering (NIBIB), RADx will leverage the NIH POCTRN to accelerate the development, validation, and commercialization of innovative point-of-care and home-based tests that can detect SARS-CoV-2, so that the public can safely return to normal activities. Its goal is to deploy millions of tests per week by fall 2020.

The program is structured to provide escalating support to awardees in a four-phase gated manner, although more advanced tests may skip phases.

- **Rolling review:** An external expert panel reviews applications for technical, clinical, regulatory, and commercialization feasibility.
- **Phase 0:** Health care and commercialization experts identify risk factors that may impede rapid deployment, milestones to address risk, and resources needed to accelerate success of the proposed tests and then develop a two-phase work package.
- **Phase 1:** Project teams work toward meeting the established milestones, with financial, technical, clinical, and business support from RADx.
- **Phase 2:** Project teams perform the full range of activities needed to distribute the test to the public, with a substantial budget for large-scale manufacturing and distribution.

NIBIB released the Request for Proposals on April 28, 2020. Of the hundreds of proposed projects, four have advanced to Phase 1.


NIH
NIBIB
NHLBI
Atlanta Center for Microsystems-Engineered POCT (ACME)
Center for Innovation in POCT for HIV/AIDS at Northwestern (C-THAN)
Center for POCT for Sexually Transmitted Diseases at JHU
Center for Advancing POCT in Heart, Lung, Blood and Sleep Disorders (CAPCaT / UMMS)
Point of Care Technology Research Network (POCTRN)
Consortia for improving Medicine through Innovation and Technology (CIMIT) MGH/HARVARD
RADx
TEST VALIDATION CORE
LARGE SCALE DISTRIBUTION CORE
CLINICAL STUDIES CORE

RADx has distinct cores for test validation, large-scale distribution, and clinical studies (see figure). The Clinical Studies Core (CSC) is responsible for designing and overseeing the evaluation of point-of-care (POC) diagnostics in rigorous clinical studies.

The CSC consists of an Administrative Working Group and five teams, the latter of which will do the following:

- The **Study Management Team** will develop the clinical trial infrastructure (e.g., write the master protocol and modules based on populations/settings or tests, identify a lab and process for parallel gold standard testing).
- Working in parallel, the **Study Design and Analysis Team** and **Community Engagement Equity Team** will ensure equity in study design and enrollment.
- The **Study Logistics Team** will establish the data coordination center and will ensure 21 CFR Part 11 compliance.
- The **Human Subjects and Oversight Team** will develop IRB templates and establish DSMBs.

The CSC is seeking platforms that can rapidly launch studies in multiple settings. One example is the NIH-supported Eureka Research Platform. Developed by the University of California, San Francisco, this direct-to-participant platform enables efficient mobile health research. The CSC is also engaged in discussions with FDA to ensure emergency use authorization (EUA) requirements are incorporated into study protocols.

In writing the master protocol, the CSC is considering numerous test features and study variables. Test features include sample type and mode of collection, definition of gold standard, and clinical status of subjects. Study variables include use cases and settings, test performance, adherence, safety, results reporting, and sample transport. Potential use cases and settings are as follows:

- Large-scale, semi-contained: manufacturing plants, large schools, large event gatherings
- Small-scale, semi-contained: day care centers, schools, businesses closed to the public, prisons
- Large-scale, public: large retail stores, transportation networks, large community buildings
- Medium- or small-scale public: retail, restaurants, rural community buildings
- Health care: retail health, MD offices, testing sites, residential communities
- Home: individual home use

Discussion

The home is the most challenging use case. It is highly unlikely that an individual can perform a nasopharyngeal swab on themselves. Therefore, other types of tests (e.g., saliva) will be preferred. Other considerations for home use include compliance, interpretation of results, reporting of results, and follow-up and support if a test is positive for SARS-CoV-2.

The Test Validation Core will undertake pre-EUA activities and will submit an EUA request to FDA, so the CSC expects to be "handed" a test with an EUA designation. FDA representatives are prepared to provide support that accommodates RADx's aggressive timeline. Like RADx and ACTIV, FDA would like outpatient trials to be as "low touch" as possible and is developing a testing template to supplement its at-home sample collection template.

The discussion also covered the following topics:

- RADx's current focus is on domestic trials, but it is engaging strategic partners with global networks.
- RADx will consider a combination test that detects (1) virus and (2) antibodies from a previous SARS-CoV-2 infection. It will not accept antibody testing alone.
- Tests will move through the stages on a rolling basis. Depending on the timing, study participants may use several tests at once, including the gold standard, which would minimize the number of participants needed and allow for participants to compare their experiences across tests.
- The Eureka Research Platform has established a COVID citizens science project, wherein individuals sign up via an app to self-monitor for symptoms. Many of these individuals have expressed a willingness to participate in research, forming a potential e-cohort.

A next step is to consider how ACTIV and RADx can collaborate and support each other's goals.

General WG Updates

The WG Co-Chairs will report the WG's progress to the Executive Committee on June 3, including showing a video demonstration of the geotracking dashboard.

The dashboard now includes an overlay of the predictive data from the University of Pennsylvania. In addition, for each network, the dashboard reports the number of sites that completed the site survey, the number of sites reported on the network rosters, and a response rate.

The WG Co-Chairs and Dr. Tountas are creating "messaging" about the value the CTC WG can add to other WG efforts.

Appendix A: Participants List

WORKING GROUP MEMBERS

Lionel Bascles, PhD, *Senior VP, Global Head of Clinical Sciences & Operations, Sanofi*

Myron Cohen, MD, *Associate Vice Chancellor for Global Health and Medical Affairs, Director, Institute for Global Health & Infectious Diseases, University of North Carolina Chapel Hill*

Larry Corey, MD, *Professor and Principal Investigator, University of Washington and HIV Vaccine*

Victoria Davey, PhD, MPH, *U.S. Department of Veterans Affairs*

Elizabeth Desrosiers (Co-Chair), MS, PMP, *Executive Director, Clinical Sciences and Study Management, Merck*

James Dickens, *Program Manager, National Center for Advancing Translational Sciences*

James Doroshow, MD, *Director of the Division of Cancer Treatment and Diagnosis, National Cancer Institute*

David Goff, MD, PhD, *Director, Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute (NHLBI)*

Michael Kurilla (Co-Chair), MD, PhD, *Director – Division of Clinical Innovation, National Center for Advancing Translational Sciences (NCATS)*

George Mensah, MD, *Director, Center for Translation Research & Implementation Science, National Heart, Lung, and Blood Institute (NHLBI)*

Seema Nayak, MD, *Director, Office of Clinical Research Resources, National Institute of Allergy and Infectious Diseases (NIAID)*

Manizhe Payton, *Director, Office of Clinical Site Oversight, National Institute of Allergy and Infectious Diseases*

Laura Resnansky, *Vice President, Global Head of Clinical Operations – Immunology, Infectious Diseases, Ophthalmology and Neuroscience, Genentech*

Christine Sizemore, PhD*, Fogarty International Center*

Michael Vincent, MD, PhD, *Senior Vice President, Chief Scientific Officer of Inflammation and Immunology Research and Development, Pfizer*

Gail Weinmann, MD, *Deputy Director, Division of Lung Diseases, National Heart, Lung, and Blood Institute*

INVITED PARTICIPANTS

Jue Chen, PhD, *Program Director, National Heart, Lung, and Blood Institute (NHLBI)*

Michelle Culp*, Office of Science Policy, NIH*

Ellen Gadbois, PhD, *Program Lead, Emerging Biotechnology Policy, NIH Office of Science Policy*

Laura Gibson, MD*, Associate Professor, University of Massachusetts Medical School*

Erin Iturriaga, PhD, *Program Officer, National Heart, Lung, and Blood Institute (NHLBI)*
Dermot Kenny, *Global Head of Data Operations, Novartis*
Stephanie Lemon, PhD, *Professor, University of Massachusetts Medical School*
David McManus, MD, *Professor, University of Massachusetts Medical School*
Tom Oswald, *University of Massachusetts Medical School*
Ashley Parker, PhD, *Special Assistant to Acting Chief of Staff to the NIH Director, National Institutes of Health*
Felicia Qashu, PhD, *Program Leader, Office of Strategic Coordination, National Institutes of Health*
Yves Rosenberg, MD MPH, *Branch Chief, National Heart, Lung, and Blood Institute (NHLBI)*

FNIH STAFF

Karen H. Tountas, PhD, *Scientific Program Manager, Science*
Jonathan Wachtel, *Manager, Deloitte*

Nancy Tuvesson, MBA, *Writer, Rose Li and Associates, Inc.*

High-Level Meeting Summary

Action Items

1. In vitro sub group members to continue working on their assigned sections of the manuscript
2. Rosa to update and send meeting invites for the new sub groups
3. Joe to schedule meeting with (b)(4) team to further discuss harmonization of the Pandemic Response SOPs

For further discussion

1. The WG will do a literature review to understand where there are gaps in knowledge that warrant additional support from ACTIV

The Preclinical Working Group (WG) met to finalize the goals and membership of its new sub-WGs and determine the logistics involved in incorporating human tissue data into preclinical objectives. Dr. Joe Menetski informed the WG that the drug repurposing manuscript and updates to the animal model inventories are successfully moving forward at a rapid pace.

Preclinical sub-WG Goals and Composition

Because they have largely accomplished their remit, the *In Vitro* and *In Vivo* sub-WGs will be replaced with four new sub-WGs: 1) Data Knowledge and Implementation, 2) BSL 3/4 Network Design, 3) Preclinical Agent Prioritization, and 4) *In Vivo* Strategy.

- Group 1 will add inventory of assay and animal models identified by ACTIV to the established NCATS Open Science Data Portal (i.e., COVID-19 data that are not currently included in the portal and have been deemed relevant by the WG) as well as create the infrastructure to collect data for those models.
- Group 2 will enable the creation of a virtual network of *in vivo* and *in vitro* facilities that can support research activities required to advance preclinical agents to the clinic. This coordination may be straightforward for NHP coordination, as there is an existing network of the National Primate Research Centers, while coordination may be more complex for *in vitro* facilities and small animal facilities, which do not already have an existing network structure and consist of many independent public and private research groups.
- Group 3 will define the process for assessing ("triaging") preclinical compounds and coordinating with the clinical WG prioritization committee. Dr. Kara Carter suggested creating three subgroups for this group: 1) antivirals, 2) immunomodulators, and 3) other promising therapeutics, such as anticoagulants and complement modulators. Group 3 may also pair Clinical and Preclinical WG members that are assessing similar categories of compounds to collaboratively prioritize and triage where necessary specific therapeutics.

- Group 4 will support the implementation of ACTIV's nonhuman primate and small animal strategies, including master protocols, funding requirements, prioritization of models for each compound (e.g., mouse, hamster, or African Green monkey), and, potentially, how to align human and NHP master protocols. The in vivo strategy group will also decide the most reasonable way to get human samples analyzed for COVID-19 disease characteristics.

WG members identified the groups to which they could most contribute, and a preliminary member list was formed (See table at the end of the document). The prioritization sub group will also leverage the external (non-ACTIV) subject matter expert panel to support the compound prioritization bases on preclinical data. Drs. Christine Colvis or John Young, will aim for at least one of them to attend each of the sub-WG meetings (and relevant meetings with other ACTIV WGs) to maintain cohesive communication throughout the WG and between the WG and ACTIV leadership.

Incorporating Clinical Data to Advance Preclinical Objectives

In the previous Preclinical WG meeting, members discussed the nuances of using data from human tissue samples to help validate animal models and, thus, improve the translation of results from the models to human COVID-19 disease. While comprehensive human data collection is valuable, clinics trials must not be further overburdened by requests for tissue collection for research purposes. To minimize burden on patients and health care providers, the ACTIV Clinical WG is limiting its data collection to samples easily (and already) obtained, such as blood. The WG can also use existing tissue archives (i.e., biobanks) to drive validation of animal models studies and to better understand disease. It must also incorporate research findings from academic and private institutions. However, because these external data would come from studies outside the ACTIV master protocols, additional validation studies may be required.

Ultimately, the WG must obtain a literature review of existing human disease data to identify knowledge gaps related to COVID-19 that could benefit from public-private partnership projects.

Collaborating with (b) (4)

(b) (4) team has also been working on screening SOPs to accelerate compounds. Given our plan to publish these SOPs, we are scheduling a meeting with (b) (4) teams to exchange SOPs and identify ways to consolidate the SOPs before sharing with the field

WG members who will meet representatives from the (b) (4) will likely include at least Drs. Rosa Maria Alvarez, Kara Carter, Christine Colvis, Michael Diamond, Ken Duncan, Joe Menetski, David Payne, John Young. The WG and (b) (4) will share information about their COVID-19 approach.

Next Steps

The WG organizers will establish a single weekly WG meeting (each Wednesday) and single weekly sub-WG meeting to commence next week. The WG organizers will also schedule a meeting with representatives from (b) (4) and finalize sub-WG membership.

Sub Group Assignments

Please email Rosa Alvarez ((b) (6) if you would like to change your sub group assignment

Initiatives (1 meeting per week + ad-hoc)	**Key Activities**	**Co-chair Leads**	**WG Members**
Data knowledge portal Implementation: What is the future state of the of data collection, access and curation?	Define of ACTIV requirements to implement in NCATS Data Portal •Data Requirements (and visualization of inventories) •Animal Model inventory considerations including FOIA, location (NCATS or Tulane NPRC), etc. •Process for data collection and curation •Access/ Viewing Rights •Staff and funding requirements	Primary: Christine Colvis Secondary: John Young	**Liz Ottinger** **Sam Jonson** Jay Grobler Cat Lutz Judith Hewitt Clint Florence Greg Gatto Yuao Zhu Jay Rappaport
Testing BSL 3 / 4 site network design (in vitro and in vivo; non-NHP)	Define strategy to implement network of sites •List of sites or network held together by an NIH mechanism •one or two different networks (in vitro and in vivo) •Harmonization of assays (Interdependency w/ Portal) •Access to site capabilities (e.g. Transcriptomics) •Funding	Primary: John Young Secondary: Christine Colvis	**Liz Ottinger** **Judith Hewitt** Greg Gatto Michael Diamond Steve Mason Ralph Baric
Preclinical agent Prioritization Process	Define staged process for triaging compounds and handoffs between WGs. For example: •Rapid triage: Triage sponsor to generate more data •Preclinical panel: Additional clarity on additional preclinical data required (in vivo vs. in vitro) •Clinical Panel: Data package is complete; go straight to clinic	Primary: John Young Secondary: Christine Colvis	**Prabha Fernandes** **Greg Gatto** **Annaliesa Anderson** Michael Diamond Kara Carter Jay Grobler Tomas Cihlar Josh Fessel Tony Punturieri

In vivo Strategy Implementation	Support implementation of ACTIV's NHP Strategy • Whitepaper, NHP estimates, NHP Protocol • ACTIV therapy prioritization process for NHPs • Funding requirements, control center • Align human and NHP master protocol • Provide an infrastructure to get human samples analyzed for COVID-19 disease characteristics	Primary: Christine Colvis Secondary: John Young	Jay Rappaport **Nancy Haigwood** Srinivas Rao Isis Kanevsky Cat Lutz **Clint Florence** Marc Charette Sheri Hild

Appendix A: Participants List

WORKING GROUP MEMBERS

Peter Adams, PhD, *BARDA*

Annaliesa Anderson, PhD, *Vice President and CSO Bacterial Vaccines, Pfizer*

Ralph Baric Professor, PhD, *Dept. of Epidemiology and Dept. of Microbiology and Immunology, UNC Chapel Hill*

Kara Carter, PhD, *Senior Vice President Infectious Disease, Evotec*

Marc Charette, PhD, *Division of Cardiovascular Diseases NIH, NHLBI*

Tomas Cihlar, PhD, *VP, and Head of Virology, Gilead*

Christine Colvis, PhD, *Director, Drug Development Partnership Programs, NCATS*

Damon Deming, PhD, (not in attendance) *Virologist, Division of Antiviral Products, Office of New Drugs, FDA*

Michael Diamond, MD, PhD, (not in attendance) *Professor, Depts. of Medicine, Molecular Microbiology, Pathology & Immunology, Washington University*

Ken Duncan, PhD, *Gates Foundation*

Prabhavathi Fernandes, PhD, *Retired, most recently led biotechs Cempra and DarPharma*

Josh Fessel, MD, PhD, *Division of Lung Diseases NIH, NHLBI*

Clint Florence, PhD, *Program Officer, Research Resource Section, OBRR, DMID, NIAID*

Greg Gatto, PhD, *Drug Development Regulatory Project Leader, RTI*

Jay Grobler, PhD, *Director, Infectious Disease Biology, Merck*

Nancy Haigwood, PhD, *Director and Professor, Oregon National Primate Research Center, OHSU*

Judith Hewitt, PhD, *Deputy Director, Office of Biodefense, Research Resources and Translational Research, NIAID*

Samantha Jonson, MPS, *Special Assistant to the Director, NCATS*

Cat Lutz, PhD, *Senior Director, Mouse Repository & In Vivo Pharmacology, Rare and Orphan Disease Center, Jackson Laboratory*

Frank Nestle, MD, (not in attendance) *Global Head of Immunology Therapeutic Research Area and Chief Scientific Officer North America, Sanofi*

Liz Ottinger, PhD, *Project Manager, NCATS*

David Payne, PhD, DSc, *Vice President & Head, Medicine Opportunities Research Unit, GSK*

Louise Pitt, PhD, *Director, Center for Aerobiological Sciences, USAMRIID*

Tony Punturieri, MD, PhD, *Division of Lung Diseases NIH, NHLBI*

Srinivas Rao, MBA, PhD, (not in attendance) *Global Head Translational In Vivo Models, Sanofi*

Jay Rappaport, PhD, *Director and Chief Academic Officer, Tulane Primate Center*

John Young, PhD, *Global Head Infectious Diseases and Vice President, Roche*

INVITED PARTICIPANTS

Ellen Gadbois, *Program Lead, Emerging Biotechnology Policy, NIH Office of Science Policy*

Sheri Hild, PhD, *Program Director for the National Primate Research Centers (NPRCs) at Office of Research Infrastructure Programs, NIH*

Ashley Parker, PhD, *Health Science Policy Analyst, NIH*

Brett Tolman, MA, *Strategy Manager at Deloitte*

Felicia Qashu, PhD, *Program Officer at National Institutes of Health*

FNIH STAFF

Stacey Adam, PhD, *Director, Cancer, Research Partnerships, FNIH*

Joseph P. Menetski, PhD, *Associate VP of Research Partnerships, FNIH*

Michael Santos, PhD, *Associate Vice President, Science, FNIH*

Rosa Maria Alvarez, PhD, *Senior Consultant*, *Monitor, Deloitte*

Benjamin Stratton, PhD, *Senior Consultant, Deloitte*

David Frankowski, PhD*, Writer, Rose Li and Associates, Inc*

Appendix B: Chat Transcript

From Prabha to Everyone: 10:21 AM

What about other animal models?

Prabha

From Josh Fessel (NIH/NHLBI) to Everyone: 10:22 AM

As the subgroups have been described, I think I could best contribute to the Preclinical Agent Prioritization Process subgroup. If I were to express a secondary choice, I think it would be the In Vivo Strategy Implementation subgroup.

From Josh Fessel (NIH/NHLBI) to Everyone: 10:26 AM

That's why I like to use the chat. ;)

From Prabha to Everyone: 10:28 AM

How about a compound availability, CMC group ?

Prabha

From John Young to Everyone: 10:29 AM

Hi Prabha

I expect that this would be part of the prioritisation group

?

From Kara Carter to Everyone: 10:29 AM

agreed

From Prabha to Everyone: 10:32 AM

Ok.. that is good since we e know the info

Preclinical prioritization group lead is fine. Prabha

From annaliesa to Everyone: 10:33 AM

I'm happy to help Prabha on the prioritization team. My sound isn't working today

From Prabha to Everyone: 10:33 AM

Thx for the help!

Prabha

From Kara Carter to Everyone: 10:36 AM

I suggest we have 3 substreams for the prioritization group that follow on the compound funnels we created: 1) antivirals 2) immunomodulators 3) others including complement and coagulation

From Prabha to Everyone: 10:36 AM

You could get someone from our expert panel to help on Clinical Prabha

From John Young to Everyone: 10:36 AM

This mirrors the Clin Tx group :)

(The same sub streams)

From Josh Fessel (NIH/NHLBI) to Everyone: 10:56 AM

I would add to John's idea of an overview of existing data (which I think absolutely is key!) is at least some assessment of the quality of that data. I'm not sure how many decisions should be made based on a really cool multiomics study done in, say, n = 5 or something.

From John Young to Everyone: 10:57 AM

Completely agree Josh. QC will be key!

High-Level Meeting Summary

The Clinical Trial Capacity Working Group (CTC WG), co-chaired by Elizabeth Desrosiers and Michael Kurilla, convened to receive updates about WG activity and to review the current version of the geotracking dashboard.

The CTC Recommendations Committees will meet on May 31 to develop recommendations for a lead network for ACTIV-1 as well as additional networks/sites and innovations for ACTIV-2 and ACTIV-3.

The Deloitte team is identifying missing sites by mapping site survey responses to network survey responses and rosters. It will then plot those sites on the geotracking dashboard map, which will provide a better representation of geographic reach. That reach will also become more evident when the CRO and SMO data are added to the dashboard. Finally, the team is exploring an overlay of data on peak number of hospitalizations, derived from a University of Pennsylvania predictive model.

Below is a summary of the key discussion themes.

General WG Updates

To date, the WG has received survey responses from 50 networks, 558 sites, and 33 contract research organizations (CROs)/site management organizations (SMOs). Ms. Desrosiers recently sent a survey to (b) (4)

The CTC Recommendations Committees attended meetings of the ACTIV-2 and ACTIV-3 Operations teams on May 27. The Recommendation Committees will meet on May 31 to develop recommendations for a lead network for ACTIV-1 as well as additional networks/sites and innovations for ACTIV-2 and ACTIV-3. Discussions with the Therapeutics (TX)-Clinical WG and Operation Warp Speed revealed that BARDA may be asked to issue a task order to a CRO in the Clinical Studies Network to run the ACTIV-1 trial.

The Innovations Sub-WG should consider innovations for the ACTIV-2 trial, which the TX-Clinical WG aims to design to be as low touch an environment as possible.

Dashboard Review and Feedback

The Deloitte team is working to provide non-NIH WG members with access to the geotracking dashboard. The team reviewed the current version of the dashboard and highlighted ongoing work, which includes: (1) grouping the survey responses to improve the filtering process; (2) exploring an overlay of data on peak number of hospitalizations, derived from a University of Pennsylvania predictive model; and (3) identifying missing sites by mapping site survey responses to network survey responses and rosters. It will then plot those sites on the map, which will provide a better representation of geographic reach. That reach will also become more evident when the CRO and SMO data are added to the dashboard.

Current dashboard limitations include the inability to (1) filter networks by adult vs. pediatric focus and (2) assess a network's ability to either sweep in patients from rural communities or to deploy resources to rural communities.

The team confirmed the following:

- The dashboard map currently depicts only those sites that responded to the site survey (25-30% response rate).
- The capacity data reflect the largest population recruited by each site for outpatient and inpatient (ICU and non-ICU) trials.
- Users will be able to filter for multiple networks and to download the data in various formats.
- The Deloitte team can incorporate additional epidemiological data sets (e.g., seroprevalence data) as they become available.
- The team can enrich the existing raw data, provided there is a clean way to do so.

A next step is to identify the top 10 or 12 survey questions, so that the Deloitte team can include them in the dropdown menu.

Appendix A: Participants List

WORKING GROUP MEMBERS

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Myron Cohen, MD, *Associate Vice Chancellor for Global Health and Medical Affairs, Director, Institute for Global Health & Infectious Diseases, University of North Carolina Chapel Hill*

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Ashley Parker, PhD, *Special Assistant to Acting Chief of Staff to the NIH Director, National Institutes of Health*

Felicia Qashu, PhD, *Program Leader, Office of Strategic Coordination, National Institutes of Health*

John Young, *Global Head of Infectious Disease and Vice President, Roche*

FNIH STAFF

Stacey Adam, PhD, *Scientific Program Manager for Cancer, Foundation for the NIH (FNIH)*

Kevin Footer

Stephanie James, PhD, *Senior VP of Science*

Ethan Jones

Michael Santos, PhD, *Associate Vice President, Science*

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Karen H. Tountas, PhD, *Scientific Program Manager, Science*

Jonathan Wachtel, *Manager, Deloitte*

Nancy Tuvesson, MBA, *Writer, Rose Li and Associates, Inc.*

Action Items

- WG members are encouraged to recommend potential users from their networks to test the Home Nursing Playbook and to suggest ways to disseminate the final version.
- WG members are encouraged to rank their top five services for playbook buildout for both the inpatient and outpatient setting, using a survey that will be distributed by FNIH staff.

High-Level Meeting Summary

The Clinical Trial Capacity Working Group (CTC WG), co-chaired by Elizabeth Desrosiers and Michael Kurilla, convened to receive general WG and geotracking dashboard updates and learn about a Home Nursing Playbook being developed for ACTIV clinical trials.

Future considerations for this WG that emerged from the Leadership Team meeting are (1) the need for policies and procedures to provide broader access to the dashboard and (2) whether to further expand the clinical trial network inventory beyond the United States.

Teams at Merck and Novartis are developing a Home Nursing Playbook that combines guidance and documents to support networks and sites onboarding of home nursing services. Playbooks for other key services can be developed, based on WG preferences.

Below is a summary of the key discussion themes.

General WG Updates

Ms. Desrosiers reported that the demonstration of the geotracking dashboard was well received by the Leadership Team members and the other WG Co-Chairs, which highlights the need for policies and procedures to provide broader access to the dashboard (e.g., network staff who might not be on the ACTIV Project roster, other organizations engaged in parallel efforts). Leadership Team members asked about the WG's plans to expand the clinical trial network inventory beyond the United States in anticipation of large-scale vaccine trials, which should be a future topic for WG discussion.

Home Nursing Playbook

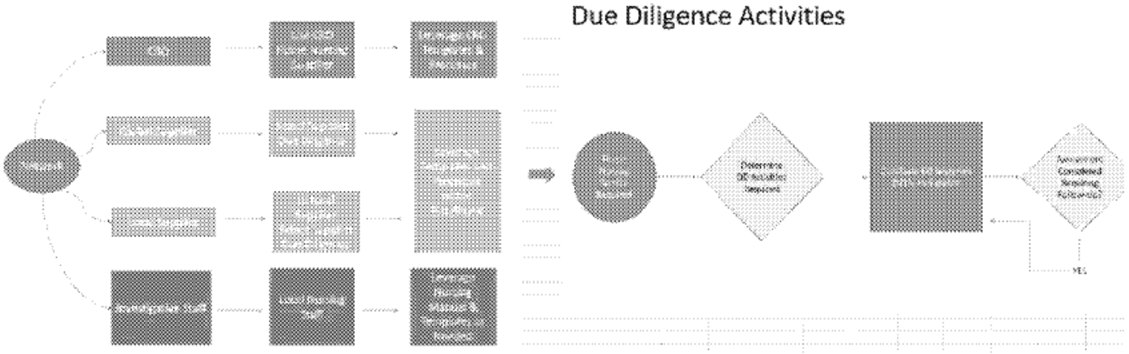
Ms. Desrosiers and Ms. Kelly and their her colleagues at Merck and Novartis, respectively, are developing a Home Nursing Playbook to be used by ACTIV clinical trial teams, as appropriate, that combines guidance documents, supplier qualification and due diligence documents, and other information to support onboarding of home nursing services to support COVID-19 trials.

The Playbook is in Excel, which is an easy-to-share format, but will be made more user-friendly before it is shared. The Excel workbook has separate tabs for the following information:

- Global Home Nursing Contact List

- Home Nursing Services and Lead Times
- Home Nursing Country Coverage
- Home Nursing Activities
- Templates (e.g., due diligence, informed consent, COVID-19 home nursing guidelines)

The playbook includes a high-level flowchart of due diligence activities, which may vary based on local requirements. In the Playbook, each shape in the flowchart (below) is hyperlinked to relevant detailed information.


Due Diligence Activities
CRO
Investigator Staff
Local Nursing Staff
Determine DD Activities Required
Activities Completed Requiring Follow-up?
YES

The WG agreed that this playbook will be a very useful tool. WG members are encouraged to recommend potential users from their networks to test the playbook and to suggest ways to disseminate the final version.

The Home Nursing Playbook serves as an example for the creation of other playbooks that can be created for other types of services. The Innovations Sub-WG identified key services to consider for playbook buildout.

- Remote monitoring
- Mobile nursing
- Investigator portal
- Telehealth
- eConsent
- Site training/tools (e.g., Teckro)
- Sample handling and tracking
- eCOA BYOD/Hybrid

WG members are encouraged to rank their top five services for both the inpatient and outpatient setting, using a survey that will be distributed by FNIH staff.

Dashboard Update

Using the live geotracking dashboard, Mr. Wachtel highlighted updates to the network and CRO views and filters, demonstrated the export process, and walked through a use case. The work to add sites identified via network rosters is ongoing. A WG member requested that exports to

Excel include columns for city, state, country, and point of contact (preferably the PI). Another WG member asked about the status of models that predict number of hospitalization cases; Dr. Kublin and colleagues are working on integrating a number of models to predict cases and incidence to create an ensemble projection. He will report on the status of this effort during the June 16 WG meeting.

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FNIH STAFF

Stacey Adam, PhD, *Director, Cancer*

Karen H. Tountas, PhD, *Scientific Program Manager, Science*

Jonathan Wachtel*, Manager, Deloitte*

Nancy Tuvesson, MBA, *Writer, Rose Li and Associates, Inc.*

High-Level Meeting Summary

The Vaccines Working Group (WG) invited Dr. Matt Biggerstaff to present on the CDC approach to forecasting COVID-19 incidence and outcomes. He provided an overview of forecasting efforts and detailed the CDC's work to assess disease hotspots and create short- and long-term forecasting models.

COVID-19 Forecasting Presentation

Forecasting Overview

The CDC Modeling Task Force, led by Dr. Rachel Slayton, uses a variety of information--such as national or state-wide disease cases and mortalities, seasonality trends, and adherence to medical or policy-based recommendations (e.g., social distancing)— to forecast epidemiological trends. Many of the parameters of the forecasting models are unknown. For example, typically new influenza cases decline in the summer, but effects of seasonality on COVID-19 are unknown. Similarly, researchers do not know the effects of lifting social distancing policies. However, forecasting can provide estimations for future trends that can help shape policy changes and inform clinical trials.

Predictive modeling is particularly important because recent studies have reported that approximately 90 percent of the United States population remains susceptible to infection. Studies have indicated that 70 percent of the United States population must be immune before transmission rates will decrease significantly. The CDC has developed a resource that lists all ongoing geographic seroprevalence studies and their results so the public remains informed.

Hotspots

One major goal of the CDC's Modeling Task Force is to identify COVID-19 incidence 'hotspots' and assess their future burdens (or likely longevity). Thus far, this team uses state-level disease case and mortality information to assess significant increases over a time period of 3 days to 2 weeks.

'Hotspot' assessment has been impacted by rapid increases in testing, including of asymptomatic patients, and less frequent data reports (states previously updated data reports daily, but have shifted to 2 to 3 times each week). Dr. Biggerstaff noted that disease case and mortality counts are standardized across the United States, making these data the most reliable (even with testing and reporting changes); however, hospitalization reports are not standardized and typically are less reliable. Limited demographic information is available for cases.

The CDC assessed the preliminary results from its 'hotspot' forecasting approach and found that only 50 percent of *emerging* outbreaks identified by the best algorithm continued into the next week, whereas over 80 percent of the top-100 counties in absolute burden remain in the top 100 during the next week. Therefore, the highest-incidence locations in the US are likely to remain so because of a lack of tools to rapidly reduce incidence.

Short-Term Modeling

Dr. Biggerstaff presented two 4-week national COVID-19 mortality forecast graphs: (1) one showed 15 distinct institutional forecasts estimating cumulative reported deaths during June compared to reported cases from April to May and (2) the second overlaid that graph with an ensemble forecast, which combines all 15 institutional forecasts into one model. The ensemble forecast generally performs as well as the best individual models. The cumulative mortality models are relatively tightly clustered with no outliers. The CDC has also reported state-level forecasts, which tend to be more variable between models with larger uncertainties than national forecasts, in part reflecting noisier data at the state level.

Dr. Biggerstaff also presented a short-term hospitalization forecast graph, which had high levels of variation between the two models displayed (i.e., Columbia University and Georgia Institute of Technology). One model predicted that hospitalizations would decrease, whereas the other predicted they would increase; in addition, the span of uncertainty was large. The CDC is working with the National Healthcare Safety Network (NHSN) to standardize hospitalization reporting to include a state-level report on the number of current inpatients suspected to have COVID-19. That data set just became available.

Long-Term Modeling

Dr. Biggerstaff presented examples of long-term modeling projection scenarios depending on changes in social distancing requirements, opening of schools, and comprehensive testing and contact tracing. If the United States returns to pre-COVID-19 baseline activities (i.e., no social distancing or stay-at-home orders) during August, the cumulative incidence of infection by the end of 2020 will increase to 75 percent. In a scenario of transition from restrictive to moderate social distancing policies, the cumulative incidence will increase to 60 percent (or 47 percent if schools do not reopen in September). With comprehensive testing and tracing measures, the cumulative incidence would increase to 30 percent (or 24 if schools do not reopen). All of these scenarios predict substantial incidence rates in the US through the summer and fall.

Conclusions

Compared to other diseases, forecasting COVID-19 trends is especially difficult because of the ongoing societal and policy changes occurring throughout the United States. However, the CDC has developed many resources to illustrate population immunity, currently active hotspots, short-term trends in COVID-19 activity, and scenarios to inform future activity, which are all available on the CDC's website.

Discussion

Participants discussed whether the granularity of forecasting could extend to more local levels (smaller than states), which would allow researchers to choose specific clinical trial sites within counties with sustained outbreaks. Dr. Biggerstaff noted that some groups are working at the county level, but data reporting becomes more varied and noisier as geographical locations narrow (i.e., from nation to state to county). The current focus is at the national and state level, but the CDC wants to get to smaller geographic areas, such as metro areas, but know that it's hard to get to that level. It is particularly difficult to identify counties that are going to have rapid growth in incidence rates, but the counties with the highest absolute incidence numbers tend to remain among the highest incidence counties in the subsequent weeks.

Predictions at state and local levels are influenced by potential variability in differences in policies in different locations, and policy and behavioral responses to peaks in incidence, which are highly uncertain. The way different jurisdictions responded to the spring peak in incidence may be informative for how they would respond to a fall peak. Although quantitative modeling is difficult at local levels, the qualitative trends should apply.

Dr. Biggerstaff noted that Google trips and mobility data and surveys have become standard tools to assess a region's adherence to stay-at-home policies. Areas with higher rebounds in mobility data may predict future growth in incidence rates. The CDC is also developing a predictive model to inform social distancing policies given health and economic goals.

The incremental incidence predicted due to school opening is due to a mix of pediatric infection and community spread. The data from Sweden are likely to be informative for models of school openings, but haven't been fully understood yet.

Participants discussed the impact of 'super-spreaders' on predictive models. 'Super-spreader' events have seemed to play less of a role within the COVID-19 pandemic than for SARS, but are known to have happened at times. The CDC's models do not account for heterogeneity of transmission, but if they did it may lower the predicted incidence somewhat.

Goals for the next 3-4 months include forecasting at more local levels than the state level, more analytic work on understanding growing hotspots, improving hospitalization predictions, and evaluating forecasts against data to provide feedback (including potentially extending the length of the forecast window).

Next Steps

Dr. Biggerstaff will share with Dr. Santos the slide deck presented during this meeting; Dr. Santos will then disseminate the slide deck to the Vaccines WG. The CDC modeling information is available at: https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/mathematical-modeling.html.

Dr. Santos will invite Dr. Biggerstaff to share updates to the COVID-19 forecast with the Vaccines WG in 4 to 6 weeks.

Appendix A: Participants List

WORKING GROUP MEMBERS

Kathrin Jansen, PhD, *Senior Vice President, Head of Vaccine Research and Development, Pfizer*
Douglas Lowy, MD, *Principal Deputy Director, National Cancer Institute (NCI)*
Paula Annunziato, MD, *Vice President, Vaccine Clinical Development, Merck*
Ann Arvin, MD, *Professor of Pediatrics and Microbiology & Immunology, Stanford University*
Beth Bell, MD, MPH, *Clinical Professor, Global Health, University of Washington*
Susan Buchbinder, MD, *Director of Bridge HIV , San Francisco Department of Public Health, and Professor, UCSF*
Marco Cavaleri, PhD, *Head of Biological Health Threats and Vaccines Strategy, European Medicines Agency (EMA)*
Larry Corey, MD, *Professor and Principal Investigator, University of Washington and HIV Vaccine Trials Network, and Past President and Director, Fred Hutchinson Cancer Research Center*
Gregory Glen, MD, *President, Research and Development, Novavax*
Barton Haynes, MD, *Director, Human Vaccine Institute, Duke University School of Medicine*
Peter Hotez, MD, PhD, *Dean for the National School of Tropical Medicine, Baylor College of Medicine, and Director, Texas Children's Center for Vaccine Development*
Antonio Lanzavecchia, MD, *Director, Immune Regulation, Institute for Research in Biomedicine*
Peter Marks, MD, PhD, *Director, Center for Biologics Evaluation and Research (CBER), U.S. Food and Drug Administration (FDA)*
Nelson Michael, MD, PhD, *Director, Center for Infectious Disease Research, Walter Reed Army Institute of Research*
Paul Offit, MD, *Professor, University of Pennsylvania, and Director, Vaccine Education Center, Children's Hospital of Philadelphia*
Michael Santos, PhD, *Associate Vice President, Science, FNIH*
Jonathan Seals, PhD, *Director, Strategic Science and Technology, Biomedical Advanced Research and Development Authority (BARDA)*
Brett Tolman, MA, *Strategy Manager, Deloitte*
Tal Zaks, MD, PhD, *Chief Medical Officer, Moderna Therapeutics*

INVITED PARTICIPANTS

Matt Biggerstaff, ScD, MPH, *Epidemiologist, CDC*
Myron Cohen, MD, *Director for Global Health & Infectious Diseases, University of North Carolina School of Medicine*
Michelle Culp, BSN, MPH, *Senior Advisor, Office of Science Policy, NIH*
Macaya Douoguih, MD, MPH, *Head, Clinical Development and Medical Affairs, Janssen*
Emily Erbelding, MD, MPH, *Director, Division of Microbiology and Infectious Diseases, NIAID, NIH*

Ellen Gadbois, PhD, *Program Lead, Biosafety, Biosecurity, and Emerging Biotechnology Policy Division, Office of Science Policy, NIH*

Peter Gilbert, PhD, *Biostatistician, Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center*

Paul Gillard, MD, *Senior Director, Clinical Development, GlaxoSmithKline (GSK)*

Marion Gruber, PhD, *Director, Office of Vaccines Research and Review, Center for Biologics Evaluation and Research (CBER), FDA*

Holli Hamilton, MD, MPH, *Senior Medical Officer, BARDA*

Markay Hopps, PhD*, Chief of Staff, Vaccine Research and Development, Pfizer*

Laurent Humeau, PhD, *Executive Vice President and Chief Scientific Officer, Research Engineering, and Clinical Developments, Inovio Pharmaceuticals, Inc.*

Cheryl Keech, MD, PhD, *Chief Medical Officer, Novavax*

Kenneth Koury, PhD, *Biostatistics, Pfizer*

Ashley Parker, PhD, *Health Science Policy Analyst, NIH*

Felicia Qashu, PhD, *Program Officer, Office of Strategic Coordination, NIH*

Merlin Robb, MD, *Chief Medical Advisor, Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc.*

Sandra Sitar, MS, *Director, Communications and Public Affairs, Vaccine Research Center, NIAID, NIH*

Jennifer Verani, MD, MPH, *Epidemic Intelligence Service Officer, Division of Global Health Protection, Center for Global Health, CDC*

Mike Watson, MB ChB, MRCP, AFPM, *President, Infectious Diseases, Moderna*

FNIH STAFF

Stephanie James, PhD, *Senior VP of Science, Foundation for the NIH (FNIH)*

Margaret Anderson*, Managing Director, Deloitte*

Benjamin Stratton*, Senior Consultant, Deloitte*

Bethany Stokes, MS*, Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

from Cheryl Keech to everyone:

question on how to apply the rapid changes to incorporate into the operations at a site level.

from Doug Lowy to everyone:

Can you project incidence for locations that are more granular than the state level?

from Peter Hotez to everyone:

(b) (5) [redacted]

from Cheryl Keech to everyone:

(b) (5) [redacted]

from Doug Lowy to everyone:

(b) (5) [redacted]

from Paul Gillard to everyone:

(b) (5) [redacted]

from Gregory Glenn to everyone:

WIll the high AR metro areas likley have some herd immunity or residual socail distancing that will decrease the atta rate?

from Ann Arvin to everyone:

Sweden did not close elementary/middle schools. is there information from their transmission patterns that can be used to project US school opening effects?

from Gregory Glenn to everyone:

How much do superspreader events drive the cumulative incidence

from Ann Arvin to everyone:

same question about how nursing homes, etc. drive cumulative incidence such that vaccine studies in communities will have different potential attack rates

from Paula W. to Annunziato everyone:

agree!

from Cheryl Keech to everyone:

really really helpful. we need lots of support on this!

High-Level Meeting Summary

The Therapeutics-Clinical (TX-Clinical) Working Group (WG) heard a presentation from Novartis regarding its Jakavi clinical trial, status updates from its Master Protocol Subgroup (MPSG), and an update on ACTIV-6.

Novartis Jakavi COVID Presentation

Representatives from Novartis presented on the results of the recent Jakavi clinical trial. The results are confidential and thus have not been summarized in this document.

Master Protocol Subgroup Updates

The MPSG reviewed progress on its various master protocols (ACTIV-1/-2/-3/-4/-5).

ACTIV-1: Immunomodulators (Inpatient Phase III)

ACTIV-1 has activated 34 sites (with five satellite sites) and (b) (4) . The ACTIV-1 team has selected an additional 87 sites (62 U.S. and 25 ex-U.S) and received regulatory approval in Argentina, Brazil, and Peru. It anticipates regulatory approval in Mexico will be awarded soon and aims to activate all Latin American sites during February.

The team is currently responding to FDA comments related to the ACTIV-1 statistical analysis plan and ACTIV-4A co-enrollment. ACTIV-4A interim results showed significant efficacy of the therapeutic heparin dose and thus the ACTIV-4A team is updating its protocol, which may impact ACTIV-1.

Site clinicians have noted that administering (b) (5)) is difficult when patients are transitioning from moderate to severe disease states. The I-SPY trial is evaluating CVC in an ICU setting and the ACTIV-1 team has invited I-SPY investigators to a future team meeting to discuss methods of overcoming this challenge.

ACTIV-2: Monoclonal Antibodies (Outpatient, Seamless Phase II/III)

ACTIV-2 has activated 100 sites and (b) (5) in total. The Brii Bio agent arm has (b) (5) , which is sufficient to initiate the first DSMB review. ACTIV-2 has also begun activating sites for Version 3.0 of the master protocol, which includes agents from AstraZeneca, Synairgen, and Sagent. Version 4.0 will soon be submitted to FDA for review and is expected to launch during late February. The ACTIV-2 team is currently working with (b) (5) to include their agents in Version 5.0. It is also working with multiple community groups to leverage outreach systems that operate in minority-owned barbershops in order to improve Hispanic and Black enrollment.

The team will meet with FDA next week to discuss a proposed symptom endpoint in ACTIV-2 trials.

ACTIV-3: Monoclonal Antibodies (Inpatient, Seamless Phase II/III)

ACTIV-3 has activated 39 sites and (b)(5) into Version 2.0, which includes agents from Brii Bio and GSK Vir. ACTIV-3 has also begun activating sites for Version 3.0. The ACTIV-3 team is now working to include Molecular Partners in a future version of the protocol. The team has activated one site each in Poland, Singapore, and Switzerland, but has experienced difficulties in activating additional international sites. Some issues may stem from the lack of international regulatory harmonization and the fact that ACTIV is not recognized as a prioritized national protocol; Dr. Libby Higgs noted that improving harmonization is the focus of G7 and recommended working towards recognition at the national policy level.

The team estimates the Version 2.0 futility analysis will occur during late February to early March. If the futility analysis is negative, ACTIV may need to reconsider its use of mAbs within an inpatient setting.

The team has been working with NeuroRx and Gilead to update the ACTIV-3b protocol based on FDA comments and aims to begin enrollment during February. Dr. Stacey Adam will invite a representative of ACTIV-3b to present an overview of the study during a future TX-Clinical WG meeting.

ACTIV-4: Anticoagulants (Pre-hospitalized/Hospitalized/Post-hospitalized, Phase III)

ACTIV-4's in-hospital protocol (4A) is currently halted because it achieved sufficient efficacy on its two therapeutic heparin arms. The ACTIV-4 team will soon incorporate a P2YB12 arm and re-initiate enrollment.

The ACTIV-4 pre-hospitalized protocol (4B) has activated 11 sites and 126 patients. The ACTIV-4B team is now working to expand site activation through CVS MinuteClinics (agreement to be finalized soon).

The post-hospitalized protocol (4C) received safe-to-proceed from both the ACTIV-4 DSMB and FDA. ACTIV-4C is expected to launch during February.

ACTIV-5: Big Effect Trial (Inpatient, Phase II)

ACTIV-5 has activated 13 sites and (b)(5). The ACTIV-5 team continues to identify sites and review additional agents for inclusion into future ACTIV-5 trials.

Discussion

Dr. Higgs asked what percentage effect the BET trials are required to achieve in order to determine whether agents can eventually be transitioned into ACTIV-3. Dr. Adam noted that BET trials must achieve effect sizes of 20 percent and will clarify with Dr. John Beigel the required odds ratio. Dr. Sarah Read noted that BET agents resulting in a p-value of 0.2 and below are viewed as promising because of the large effect requirement.

Dr. Higgs noted that other ACTIV trials, particularly ACTIV-4A, observed differences in efficacy within certain patient populations and noted that BET may not have sufficient sample sizes to detect efficacious signals across each patient strata; thus, the TX-Clinical WG may need to reconsider its approach to evaluating across the disease severity spectrum.

Pragmatic Trial Update

ACTIV leadership aims to launch ACTIV-6, which will be a pragmatic platform trial that aims to definitively evaluate widely available agents with potential therapeutic value for COVID-19 (most of which have previously been studied in multiple small-scale trials). ACTIV-6 will have clear endpoints, be as remote as possible, and use an updated version of existing agent selection criteria to account for real-world evidence. ACTIV aims to launch this trial within the next month and has met with multiple potential partners in recent weeks to discuss its feasibility and to solicit participation from FDA, the Critical Path Initiative, (b) (4) , [redacted] and NC3. Members of the Agent Prioritization Subteams will be invited to form a new ACTIV-6 Prioritization Subteam.

Appendix A: Participants List

WORKING GROUP MEMBERS

Neil Aggarwal, MD, *Lung Biology and Disease Branch Chief, National Heart, Lung, and Blood Institute (NHLBI)*

Samuel Bozzette, MD, PhD, *Chief Medical Officer, National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH)*

Timothy G. Buchman, MD, PhD, *Biomedical Advanced Research and Development Authority*

Joan Butterton, MD, *Associate VP, Clinical Research, Infectious Diseases, Merck & Co.*

Judith Currier, MD, *Professor of Medicine in the Division of Infectious Diseases, University of California, Los Angeles*

R. Angelo DeClaro, MD, *Division Director (Acting), Division of Hematologic Malignancies, Food and Drug Administration (FDA)*

Ruxandra Draghia-Akli, MD, PhD, *Global Head, Global Public Head R&D, Johnson & Johnson*

Elizabeth (Libby) Higgs, MD, MIA, DTM&H, *Global Health Science Advisor, National Institute of Allergy and Infectious Diseases (NIAID)*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis (WG Co-chair)*

Lisa LaVange, PhD, *Professor and Associate Chair, Department of Biostatistics, UNC Chapel Hill*

John Mellors, MD, *Professor of Medicine, Chief of Infectious Diseases Division, University of Pittsburgh*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID (WG Co-chair)*

Peter Stein, MD, *Director of Office of New Drugs, CDER, FDA*

Larry Tsai, MD, *Global Head of Respiratory and Rheumatology Product Development, Genentech*

INVITED PARTICIPANTS

Linda Armstrong, MD, *Global Head Respiratory Development Unit, Novartis*

Lorraine Bandelli, PhD, *Director, Clinical Drug Development, Novartis*

Donald Banerji, MD, *Global Health Clinical Development, Respiratory Clinical Development & Analytics, Novartis*

Diane Bonagura, MS, *Global Trial Director, Novartis*

Timothy H. Burgess, MD, MPH, *Captain, Navy*

Weihua Cao, PhD, *Associate Director of Biostatistics, Novartis*

Christine Colvis, PhD, *Director, Drug Development Partnership Programs, NCATS*

Jim Felser, MD, *Infectious Disease Specialist, Novartis*

Dave Feltquate, MD, PhD, *Global Head, Hematology Disease Unit, Novartis*

Ellen Gadbois, *Program Lead, Emerging Biotechnology Policy, NIH Office of Science Policy*

Barbara Knorr, MD, *Senior Global Program Clinical Head, Novartis*

Peter Langmuir, MD, *Vice President, Oncology Drug Development, Incyte*

Thomas Lehmann, PhD, *VP Global Program Head, Novartis*
Andrea Lerner, MD, MS, *Medical Officer, Office of the Chief of Staff, NIAID*
Robert Malone, MD, *Chief Medical Officer, Alchem Laboratories Corporation*
Revell Phillips, PhD, *Science and Technology Manager, Defense Threat Reduction Agency*
Lora Reineck, MD, *Program Director, Lung Biology and Disease Branch, NHLBI*
Ronald Reisler, MD, MPH, *Senior Clinical Advisor, Davis Defense Group*

STAFF

Stacey Adam, PhD, *Director, Cancer, Foundation for the NIH (FNIH)*

Helen Chen, PhD, *Consultant, Deloitte*
Evan Appell, *Consultant, Deloitte*
Alex Sorosa, *Business Analyst, Deloitte*

Bethany Stokes, MS, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

From Eric Hughes to Everyone: 01:39PM

welcome back Sam! hurrah!

From Sam Bozzette to Everyone: 01:40PM

Thanks!

From Libby Higgs to Everyone: 01:40PM

Really, definitely missed your sage input and humor

From Lisa LaVange to Everyone: 01:40PM

Sam -- we have missed you!

From Libby Higgs to Everyone: 01:56PM

ACTIV 3 grateful to Judy for presenting results to our site investigators yesterday.

From (b) (6) to Everyone: 01:58PM

Has (b) (4) crossed our inbox yet? I ask because of the flurry of publicity.

From (b) (6) to Everyone: 02:05PM

Hi (b) (6) - I just checked our list of survey submissions from the ACTIV portal (along with agents that we've previously reviewed) and we have (b) (5)

From Libby Higgs to Everyone: 02:07PM

Rapidly done, good job.

From Neil Aggarwal to Everyone: 02:09PM

Montreal Heart Institute

Action Items

- Mr. Kenny will ask Mr. Srinivasan about his willingness to serve on a Recommendation Committee that reviews both the ACTIV-1 and ACTIV-3 protocols.
- Dr. Tountas will add Mr. Kenny and Dr. Mensah to the Recommendation Committee for outpatient protocols.
- Drs. Adam and Tountas will coordinate invitations for Recommendation Committee members to attend the ACTIV-2 and ACTIV-3 Operations Teams meetings.
- WG members will provide Mr. Wachtel with feedback on the geotracking dashboard.
- Dr. Tountas will send via email the Excel spreadsheet with the CMO/SRO data.

High-Level Meeting Summary

Rather than establish a third CTC Recommendation Committee for the rapidly developing ACTIV-3 protocol, the WG decided to move forward with one committee for the inpatient protocols (ACTIV 1- and ACTIV-3) and one committee for the outpatient protocol (ACTIV-2), which will prevent duplication of efforts between committees.

The BARDA Clinical Studies Network (CSN), established via an IDIQ (indefinite delivery/indefinite quantity) contract in 2014, is available to ACTIV. The CSN is a consortium of five Contract Research Organizations (CROs) selected for their ability to provide a full range of services. These CROs have extensive experience working with federal government agencies. Of the eight task orders issued since the CSN's inception, three remain active and are vaccine trials. The current contract expires on September 30, 2020; however, any project or study initiated before that date will continue under this contract.

Below is a summary of the key discussion themes.

CTC Recommendation Committees

The WG recently established the ACTIV-1 and ACTIV-2 CTC Recommendation Committees. Like ACTIV-1, the rapidly developing ACTIV-3 protocol will focus on the inpatient setting. Rather than establish a third committee, the WG decided to move forward with one committee for both inpatient protocols (Davey, Goff, Nayak, and Srinivasan) and one committee for the outpatient protocol (Cohen, Davey, Payton, and Resnansky), which will prevent duplication of efforts between committees.

Discussion

Unless interested in doing so, CTC Recommendation Committee members will not serve on the protocol writing teams. However, the Innovations Sub-WG may contribute to the writing process by identifying innovations and technologies that could support certain protocol elements. The ACTIV-1 protocol is 80 percent complete, but a lead network has not been identified. The ACTIV-2 protocol is 90 percent complete and has been submitted to an internal

NIAID Concept Review Committee. ACTG will be the ACTIV-2 lead network. INSIGHT will be the ACTIV-3 lead network, with PETAL as a potential partner. Operations Teams for ACTIV-2 and ACTIV-3 have been formed and plan to first meet during the week of May 25.

BARDA Clinical Studies Network

Dr. Robert Walker presented on the BARDA Clinical Studies Network (CSN), which was established via an IDIQ contract in 2014. CSN is a consortium of five CROs (ICON GPHS, Emmes, TRI, Rho, and PPD) selected for their ability to provide a full range of services. These CROs have extensive experience working with federal government agencies. To date, eight task orders have been issued to the CSN; three remain active (H5N1, H7N9, anthrax vaccines). Although the current contract expires on September 30, 2020, any project or study initiated before the that date will continue. BARDA has recompeted the contract and expects to make new awards in September.

The CSN has successfully met many of BARDA's clinical study needs. BARDA has benefited from awarding a single study to multiple contractors. However, the quality of deliverables and services has been highly variable, and the IDIQ mechanism has been less agile than anticipated. Future enhancements include a flexible (vs. full) service model, centralized data coordinating center, long-term storage of clinical specimens and investigational products, and a standardized process for archiving study files. BARDA recently issued an RFI to the five CROs and Pharm Alom to assess their ability to perform platforms trials and operate globally. Through a COVID-related contract mechanism, BARDA can also rapidly contract with CROs outside of the CSN.

Discussion

Dr. Walker confirmed that this IDIQ vehicle is available to ACTIV. During the pandemic, the amount of time from developing to executing a task order has declined, and now stands at approximately 2 weeks for small projects. He anticipates additional CSN capacity with the new awards issued under the next contract in September.

Dashboard Update

WG members without NIH credentials will have access to the dashboard on May 28. WG members are encouraged to provide Mr. Wachtel with feedback, which will be consolidated and discussed during the group's regular meeting on May 29. The Deloitte team has not loaded CRO/SMO data; Dr. Tountas will circulate the Excel spreadsheet with those data instead.

Appendix A: Participants List

WORKING GROUP MEMBERS

Lionel Bascles, PhD, *Senior VP, Global Head of Clinical Sciences & Operations, Sanofi*

Myron Cohen, MD, *Associate Vice Chancellor for Global Health and Medical Affairs, Director, Institute for Global Health & Infectious Diseases, University of North Carolina Chapel Hill*

Larry Corey, MD, *Professor and Principal Investigator, University of Washington and HIV Vaccine*

Victoria Davey, PhD, MPH, *U.S. Department of Veterans Affairs*

Elizabeth Desrosiers (Co-Chair), MS, PMP, *Executive Director, Clinical Sciences and Study Management, Merck*

James Dickens, *Program Manager, National Center for Advancing Translational Sciences*

David Goff, MD, PhD, *Director, Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute (NHLBI)*

Michael Kurilla (Co-Chair), MD, PhD, *Director – Division of Clinical Innovation, National Center for Advancing Translational Sciences (NCATS)*

George Mensah, MD, *Director, Center for Translation Research & Implementation Science, National Heart, Lung, and Blood Institute (NHLBI)*

Seema Nayak, MD, *Director, Office of Clinical Research Resources, National Institute of Allergy and Infectious Diseases (NIAID)*

Manizhe Payton, *Director, Office of Clinical Site Oversight, National Institute of Allergy and Infectious Diseases*

Laura Resnansky, *Vice President, Global Head of Clinical Operations – Immunology, Infectious Diseases, Ophthalmology and Neuroscience, Genentech*

Christine Sizemore, PhD, *Fogarty International Center*

Michael Vincent, MD, PhD, *Senior Vice President, Chief Scientific Officer of Inflammation and Immunology Research and Development, Pfizer*

Gail Weinmann, MD, *Deputy Director, Division of Lung Diseases, National Heart, Lung, and Blood Institute*

INVITED PARTICIPANTS

Jintanat Ananworanich, MD, PhD, *Bill & Melinda Gates Medical Research Institute*

Michelle Culp, *Office of Science Policy, NIH*

Ellen Gadbois, PhD, *Program Lead, Emerging Biotechnology Policy, NIH Office of Science Policy*

Kelly Gebo, MD, MPH, *Chief Medical and Scientific Officer, All of Us Research Program*

Penny Heaton, MD, *Chief Executive Officer, Bill & Melinda Gates Medical Research Institute*

Dermot Kenny, *Global Head of Data Operations, Novartis*

Robin Mason, MS, MBA, *Clinical Project Manager, NIAID*

Robert Walker, MD, *Chief Medical Officer and Director, Division of Clinical Development, Biomedical Advanced Research and Development Authority, U.S. Department of Health and Human Services*

FNIH STAFF

Stacey Adam, PhD, *Scientific Program Manager for Cancer, Foundation for the NIH (FNIH)*

Stephanie James, PhD, *Senior VP of Science*

Michael Santos, PhD, *Associate Vice President, Science*

Benjamin Stratton, *Senior Consultant, Deloitte*

Karen H. Tountas, PhD, *Scientific Program Manager, Science*

Jonathan Wachtel, *Manager, Deloitte*

Nancy Tuvesson, MBA, *Writer, Rose Li and Associates, Inc.*

High-Level Meeting Summary

The Preclinical Working Group (WG) discussed progress made by its three subgroups: (1) BSL 3/4 Network Implementation, (2) Pandemic Response Manuscript, and (3) Preclincal/Clinical Data Survey. In addition, the WG reviewed instructions detailing ACTIV policies for handling of intellectual property (IP) from COVID-19-related submissions.

Action Items

- WG members should send Joe and Rosa any questions that may help to probe the capabilities of testing facilities interested in evaluating compounds
- Joe will consult FNIH legal counsel to obtain further details on FNIH's previous approaches to IP
- Rosa to share abstract and figures of the manuscript to anyone interested

Debrief from Subgroup Meetings

BSL 3 / 4 Network Implementation

The WG plans to list (on the NCATS OpenData Portal) a 'virtual network' of laboratories that will assist the research community in testing COVID-19 compounds using *in vitro*, small animal, and/or NHP models. The WG plans to send a formal email invitation to laboratories it has identified, in large part through NIAID, to query interest in participation. If a group is interested, the WG will send a second email to survey general facility testing capabilities (e.g., specialized techniques, capacity, throughput, and adherence to Good Laboratory Practices). The WG plans to publish the list of all laboratories included in its virtual network, along with their capabilities, which may encourage other testing facilities to join the network. All sensitive or proprietary information will not be released to the public unless otherwise specified by the applicant. If the ACTIV budget permits, the WG may also survey both the current and projected needs of these facilities to potentially provide financial support for compound testing.

The ACTIV budget will also determine the WG's level of involvement in coordinating the use of facilities in this virtual network. With additional funding, the WG may establish a coordinating center to facilitate materials and data sharing between compound manufacturers and testing facilities. This coordinating center would maintain detailed information on each testing facility to identify that which best suits the needs of each asset holder, and support facilities (as needed) (e.g., only directing compound submissions to testing facilities with available capacity). The WG, with or without an official coordinating center, may also help to establish contractual agreements (e.g., Material Transfer Agreements and Confidential Disclosure Agreements) between asset holders and laboratories to accelerate testing.

Drs. Christine Colvis and John Young will consider two separate plans to facilitate compound testing. The first plan, which *may not* require additional funding, will be to create an inventory of publicly available information about *in-vitro*, small animal, and NHP model testing facilities and their capabilities. The second plan, which *will* require additional funding, will be to create a coordinating center to operationalize logistics of transferring materials and information between production facilities and testing facilities in the virtual network.

Pandemic Response Screening Manuscript

The abstract and figures for the pandemic response screening manuscript are finalized and will be sent to editors of the following journals to gauge publishing interest: Nature Reviews Drug Discovery, PLOS Pathogens, Cell Host & Microbe, Science Translational Medicine, and Clinical and Translational Science. The figures include the compound screening funnel diagrams for antivirals, immunomodulators, complement inhibitors, and coagulation inhibitors. An additional figure has been generated comparing the traditional drug discovery process with the emergency (i.e., pandemic necessitated) drug discovery process. The article subsections are divided among subgroup members and will be harmonized when complete (first draft targeted for June 22).

A first draft of the Introduction, which compares the emergency and nonemergency drug development processes and delineates ACTIV's target patient populations (e.g., severely ill and moderately ill), has been completed. The WG wanted to emphasis that despite the speed of pandemic drug development, safety still needs to be assessed appropriately. Another topic that will be included is that initial testing during pandemic response drug development may settle for a moderately effective drug (e.g., (b) (4) [redacted], whereas subsequent rounds will involve more traditional testing and are more likely to identify highly efficacious drugs. The WG may also consider including information about how COVID-19 differentially affects individuals with specific comorbidities and about the racial disparities identified. Dr. Rosa Maria Alvarez will send the abstract and figures, as well as the journal letters, to any interested WG members.

Preclinical/Clinical Compound Data Survey

The clinical WG members sent the preclinical/clinical compound data survey to colleagues and have received seven completed compound submissions. The WG disseminated the survey to the ACTIV Executive Committee, whose members will broadly share the survey with colleagues at asset-holding institutions. WG members want to remain apprised of where the surveys are sent to avoid duplicative requests. The WG should also consider methods to broadly solicit survey responses (e.g., via industry journals) from small and potentially lesser-known companies.

Discuss Final IP Language

Dr. Srinivas Rao and legal experts from several pharmaceutical companies created a general disclaimer to inform researchers of how IP included in any ACTIV submission (e.g., therapeutic or vaccine candidates, resources, and methods or concepts) will be publicly disclosed. Guidance notes that all submissions should avoid including proprietary information without first entering into a Confidential Disclosure Agreement with ACTIV. (b) (5) [redacted]

Next Steps

WG members should send the co-chairs any questions that may help to probe the capabilities of testing facilities interested in evaluating compounds. The WG will consider ways to expand the reach of its Preclinical/Clinical survey to include lesser known companies. Dr. Joe Menetski will assess previous approaches to IP by FNIH.

Appendix A: Participants List

WORKING GROUP MEMBERS

Peter Adams, PhD, *Health Scientist, Project Officer, BARDA*

Annaliesa Anderson, PhD, *Vice President and CSO Bacterial Vaccines, Pfizer*

Ralph Baric Professor, PhD, *Dept. of Epidemiology and Dept. of Micobiology and Immunology, UNC Chapel Hill*

Kara Carter, PhD, *Senior Vice President Infectious Disease, Evotec*

Marc Charette, PhD, *Division of Cardiovascular Diseases NIH, NHLBI*

Tomas Cihlar, PhD, *VP, and Head of Virology, Gilead*

Christine Colvis, PhD, *Director, Drug Development Partnership Programs, NCATS*

Damon Deming, PhD, *Virologist, Division of Antiviral Products, Office of New Drugs, FDA*

Michael Diamond, MD, PhD, *Professor, Depts. of Medicine, Molecular Microbiology, Pathology & Immunology, Washington University*

Ken Duncan, PhD, *Gates Foundation*

Prabhavathi Fernandes, PhD, *Retired, most recently led biotechs Cempra and DarPharma*

Josh Fessel, MD, PhD, *Division of Lung Diseases NIH, NHLBI*

Clint Florence, PhD, *Program Officer, Research Resource Section, OBRR, DMID, NIAID*

Greg Gatto, PhD, *Drug Development Regulatory Project Leader, RTI*

Jay Grobler, PhD, *Director, Infectious Disease Biology, Merck*

Nancy Haigwood, PhD, (not in attendance) *Director and Professor, Oregon National Primate Research Center, OHSU*

Judith Hewitt, PhD, *Deputy Director, Office of Biodefense, Research Resources and Translational Research, NIAID*

Samantha Jonson, MPS, *Special Assistant to the Director, NCATS*

Cat Lutz, PhD, *Senior Director, Mouse Repository & In Vivo Pharmacology, Rare and Orphan Disease Center, Jackson Laboratory*

Frank Nestle, MD, (not in attendance) *Global Head of Immunology Therapeutic Research Area and Chief Scientific Officer North America, Sanofi*

Liz Ottinger, PhD, (not in attendance) *Project Manager, NCATS*

David Payne, PhD, DSc, (not in attendance) *Vice President & Head, Medicine Opportunities Research Unit, GSK*

Louise Pitt, PhD, *Director, Center for Aerobiological Sciences, USAMRIID*

Tony Punturieri, MD, PhD, *Division of Lung Diseases NIH, NHLBI*

Srinivas Rao, MBA, PhD, *Global Head Translational In Vivo Models, Sanofi*

Jay Rappaport, PhD, *Director and Chief Academic Officer, Tulane Primate Center*

John Young, PhD, *Global Head Infectious Diseases and Vice President, Roche*

INVITED PARTICIPANTS

Ellen Gadbois, *Program Lead, Emerging Biotechnology Policy, NIH Office of Science Policy*
Sheri Hild, PhD, *Program Director for the National Primate Research Centers (NPRCs) at Office of Research Infrastructure Programs, NIH*
Ashley Parker, PhD, *Health Science Policy Analyst, NIH*
Brett Tolman, MA, *Strategy Manager at Deloitte*
Felicia Qashu, PhD, *Program Officer at National Institutes of Health*

FNIH STAFF

Stacey Adam, PhD, *Director, Cancer, Research Partnerships, FNIH*
Joseph P. Menetski, PhD, *Associate VP of Research Partnerships, FNIH*
Michael Santos, PhD, *Associate Vice President, Science, FNIH*

Rosa Maria Alvarez, PhD, *Senior Consultant*, *Monitor, Deloitte*
Benjamin Stratton, PhD, *Senior Consultant, Deloitte*

David Frankowski, PhD*, Writer, Rose Li and Associates, Inc*

Appendix B: Chat Transcript

From Josh Fessel (NIH/NHLBI) to Everyone: 10:01 AM

The coffee mug game in this group is STRONG! :)

Caffeine is ordained by destiny.

From cat lutz to Everyone: 10:33 AM

I wondered about CROs, Like lovelace? Would there be a value in having CROs

From Judy Hewitt to Everyone: 10:34 AM

Yes, they'll be included at least those in the NIAID contracting pool ;-)

From (b) (6) to Everyone: 10:55 AM

Who from our end would "sign" the CDA?

From (b) (6) to Everyone: 11:00 AM

I think the question of who on the NIH side would "sign" the CDA is a good one. I think the FOIA question with respect to the NIH side is also one to think about closely (I know people are doing that, but wanted to say it specifically).

Apologies, have a hard stop at 11am. Great discussion today!

From Kara Carter to Everyone: 11:01 AM

I need to leave for another meeting. Thanks for another productive call.

From Michael Diamond to Everyone: 11:01 AM

I have a hard stop and need to sign off

From Jay Rappaport to Everyone: 11:05 AM

Got a message I have another meeting also and need to sign off. Great discussion!

High-Level Meeting Summary

The Therapeutics-Clinical Working Group (TX-Clinical WG) heard updates from both its Master Protocol and Agent Prioritization Subgroups (MPSG and APSG, respectively) and viewed a brief demonstration of a new Online Agent RFI Survey Tool, which will solicit data relevant to agent prioritization from companies with agents of interest.

Master Protocol Subgroup Updates

The MPSG presented on the designs of its various master protocols now under development:

- **ACTIV-1:** immunomodulators (selected during Wave 1 agent prioritization)
- **ACTIV-2:** mAbs—for efficacy among outpatients (agents not yet selected)
- **ACTIV-3:** mAbs—for efficacy among inpatients (agents not yet selected)

Representatives of the National Heart, Lung, and Blood Institute (NHLBI) also presented NHLBI's **ACTIV Anticoagulation Trials**, which will test three anticoagulants selected during ACTIV's Wave 1 agent prioritization.

ACTIV Anticoagulation Trials

Two ACTIV Anticoagulation Trials (one for inpatients and one for outpatients) will be led by NHLBI network teams and conducted within the NHLBI 'network of networks.' Drs. Amy Patterson and Keith Hoots presented on the rationale behind NHLBI's planned outpatient anticoagulation trial, which will include both prehospitalization and convalescent patients. Dr. Patterson noted that some ambulatory COVID-19 patients present with major thromboembolic events/vascular injuries, and that the underlying pathobiology of these events, and their associated risk factors, remain unknown. Patients exhibit systemic coagulopathy that affects every type of vasculature, which can in turn negatively affect their central nervous systems. NHLBI has therefore been coordinating with the National Institute of Neurological Diseases and Stroke (NINDS) to develop ACTIV's Anticoagulation Trials. Experts on the biology of adaptive immunity, thromboinflammation, and coagulation/coagulopathy are also contributing to its adaptive trial design.

ACTIV Anticoagulation Trials will use interventions of varying 'intensities' for prehospitalized hospitalized, and convalescent patient populations. NHLBI supplements trials with biospecimen collection and natural history studies to allow for deep phenotyping of enrolled patients, which may aid discovery of new biomarkers (e.g., for patient stratification) or new therapeutic targets.

Discussion

Dr. Judith Currier proposed that ACTIV determine the capacity of the 'network of networks' by assembling an inventory of clinical *sites*—rather than of networks—to reduce the potential for duplication of efforts (e.g., duplicative requests to collect biospecimens) as a result of one site's participation in multiple networks. Dr. Adam will escalate this request to the ACTIV Executive Committee for its potential assistance.

Dr. Timothy Buchman noted that standard of care for anticoagulation strategies has rapidly changed for COVID-19 patients—especially in inpatient settings—and that consequently natural history studies of coagulopathy in these patients need to account for infection *plus* clinical response.

ACTIV-1: Immunomodulators (Phase III)

The ACTIV-1 Writing Team/Guidance Committee, which now meets Mondays, Wednesdays, and Fridays, includes representatives from all three companies whose immunomodulators are being tested under ACTIV-1 (i.e., Janssen, Bristol Myers Squibb, and AbbVie/Allergan). Team members have agreed on (1) overarching versus agent-specific inclusion/exclusion criteria, (2) biomarkers, and (3) primary and secondary outcomes. The team is refining ACTT's overarching protocol into a standalone master protocol to better integrate agent sub-studies and later entry of molecules if desired. It is also working to identify a lead network—the team will likely enlist a contract research organization (CRO)—that can provide input on protocol drafting and logistics.

ACTIV-2: Monoclonal Antibodies (Outpatients)

ACTIV-2, a Phase II-to-III progressive master protocol for testing mAbs in COVID-19 outpatients, is approximately 80 percent completed. It is being drafted collaboratively by ACTIV, Operation Warp Speed (OWS) and the National Institute of Allergy and Infectious Diseases (NIAID), as well as the AIDS Clinical Trials Group (ACTG), which will serve as the lead network for ACTIV-2 trials. The writing team—in consultation with both the ACTIV mAb Steering Committee and the Food and Drug Administration (FDA)—has decided to require an ascending dose study prior to entry into the ACTIV-2 protocol (OWS is assessing how much assistance potential participating companies may need to conduct these studies). ACTIV-2's Statistics Team has defined simulation details and incorporated a Bayesian framework for Phase II-to-III progression to be applied after the first study. ACTIV-2's Operations Team continues to refine logistical details of implementing the protocol, with enrollment for the first investigative asset projected for the end of June.

ACTIV-3: Monoclonal Antibodies (Inpatients)

The INSIGHT Network will spearhead implementation of ACTIV-3, and NHLBI's PETAL Network is being considered as a partner for the study. The protocol will be drafted by ACTIV, INSIGHT, OWS, and NIAID. Members of the writing team are now being confirmed; this team will work closely with the ACTIV-2 writing team to harmonize the inpatient and outpatient protocols. An ACTIV-3 synopsis will be developed by the end of this week for sharing with FDA and sponsoring companies. ACTIV-3's Operations Team is established; it is communicating with the Clinical Trial Capacity WG to identify a suitable CRO as well as additional clinical sites. It will add other members to finalize logistics for protocol implementation.

Second Monoclonal Antibodies Clinical Summit

Dr. Stacey Adam noted that Dr. Janet Woodcock of FDA, who is leading OWS efforts to develop therapeutics, is working with ACTIV to convene a second mAb clinical summit to help press companies with mAbs for SARS-CoV-2 to submit their assets to ACTIV's mAb trials. Dr. Adam presented a timeline of key activities (shown below) leading up to that second summit, scheduled for the week of June 8. Whereas the initial mAb summit included all 21 companies with mAbs in development against COVID-19, this second summit will focus more narrowly on those whose agents are likely to be ready for clinical testing by the end of calendar year 2020.

Key activities	Date
☐ Complete drafts of inpatient and outpatient protocol synopses	5/29-5/31
☐ Draft target timeline for full protocols in "draft" form	6/1-6/5
☐ Establish CRO needs for lead networks, issue RFP, and select vendors	6/1-6/5
☐ Review protocol synopses with internal stakeholders and CDER	6/3
☐ Send pre-read to clinical summit attendees (including synopses)	6/5
☐ ACTIV to host clinical summit with heads of R&D	*week of 6/8*

Objectives for the summit would be to establish company interest for participation in the master protocol and the timelines by which their agents would be ready for testing.

Dr. Adam also noted that the mAb Steering Committee has requested that in addition to heads of R&D, companies' clinical development leads be asked to attend the mAb clinical summit. She will escalate that request to the ACTIV Executive Committee.

Discussion

Dr. Elizabeth Higgs recommended that representatives who can "speak for the companies" also be involved in the immediate efforts to draft the mAb protocols to ensure that companies are aligned with protocol designs. Dr. Adam expressed caution about requesting that level of involvement from companies before they have made official commitments but agreed to seek additional company representation. Several participants noted that company representatives are already included on the mAb Steering Committee and have provided useful input on both ACTIV-2 and ACTIV-3.

Dr. Joan Butterton recommended establishing a mechanism for companies to submit non-mAbs (e.g., small molecules) for consideration to be tested under another ACTIV master protocol.

Agent Prioritization Subgroup Updates

The TX-Clinical WG received updates on progress of the APSG mAb Subteam and development of the APSG Online Agent Request for Information (RFI) Survey Tool.

Monoclonal Antibody Subteam

The APSG mAb Subteam, chaired by Dr. John Mellors, began meeting this week to establish its minimum 'gating' criteria ('must-haves' and 'nice-to-knows') for considering mAbs for ACTIV-2 and ACTIV-3 testing. It is finalizing these criteria, which will be shared early next week.

Discussion

Dr. Keith Gottesdiener noted that the minimum 'gating' criteria being developed by the mAb Subteam appear to focus on what *kinds* of characteristics and data are preferred for each candidate mAb, rather than on what precise *criteria* must be met. Dr. (b)(6) (b)(5) [redacted]. For example, mAb entry criteria for a progressive Phase II-to-III study of a single dose will not be the same as those for a Phase I-to-II study that also includes dose ranging. Dr. Mellors acknowledged that the mAb Subteam did not realize that its remit was to develop such precise mAb inclusion/exclusion criteria. He and Dr. Adam agreed to clarify the Subteam's remit and revisit its 'gating' criteria.

Online Agent Request for Information Survey Tool

Dr. Benjamin Stratton of Deloitte provided a brief demonstration of the Online Agent RFI Survey Tool, noting that TX-Clinical WG members would receive a link to the RFI Survey Tool and asking that they provide any feedback or suggestions to improve it. Dr. Buchman commented that the RFI Survey Tool should expand the options under "Type of therapeutic intervention" to include more target organ systems (i.e., to remove ambiguity when respondents select 'Other').

Dr. Adam stated that a live link to the RFI Survey Tool should be ready for distribution to asset holders is targeted for May 29. This tool will become the default mechanism for companies to submit their agents for consideration for ACTIV prioritization and testing.

Appendix A: Participants List

WORKING GROUP MEMBERS

Sam Bozzette, MD, PhD, *Chief Medical Officer, National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH)*

Timothy G. Buchman, MD, PhD, *Biomedical Advanced Research and Development Authority (BARDA)*

Joan Butterton, MD, *Associate VP, Clinical Research, Infectious Diseases, Merck & Co.*

Judith Currier, MD, *Professor of Medicine in the Division of Infectious Diseases, University of California, Los Angeles (UCLA)*

Ruxandra Draghia-Akli, MD, PhD, *Global Head, Global Public Head R&D, Johnson & Johnson*

Mark Eisner, MD, MPH, *Senior VP, Global Head of Immunology, Infectious Disease, and Ophthalmology Clinical Development, Genentech*

Keith Gottesdiener, MD, *Former President and Chief Executive Officer, Rhythm*

Elizabeth (Libby) Higgs, MD, MIA, DTM&H, *Global Health Science Advisor, National Institute of Allergy and Infectious Diseases (NIAID)*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis (WG Co-chair)*

Lisa LaVange, PhD, *Associate Chair, Department of Biostatistics, UNC*

John Mellors, MD, *Professor of Medicine, Chief of Infectious Diseases Division, U. Pittsburgh*

Michael Proschan, PhD, *Mathematical Statistician, Biostatistics Research Branch, NIAID, NIH*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH (WG Co-chair)*

Daniel Ruben, PhD, *Division of Biometrics IV, CDER, FDA*

Peter Stein, MD, *Director of Office of New Drugs, CDER, FDA*

INVITED PARTICIPANTS

Neil Aggarwal, MD, *Lung Biology and Disease Branch Chief, National Heart, Lung, and Blood Institute (NHLBI)*

Timothy H. Burgess, MD, MPH, *Captain, Navy*

Christine Colvis, PhD, *Director for Drug Development Partnership Programs, NCATS, NIH*

Michelle Culp, MPH, *Office of the Director, NIH*

Ellen Gadbois, PhD, *Office of Science Policy, Office of the Director, NIH*

Mary Groesch, PhD, *Office of the Director, NHLBI*

W. Keith Hoots, MD, *Director, Division of Blood Diseases and Resources, NHLBI*

Ashley Parker, PhD, *Health Science Policy Analyst, NIH*

Amy Patterson, MD, *Chief Science Advisor and Director of Scientific Research Programs, NHLBI*

Dionne Price, PhD, *Director, Division of Biometrics IV, CDER, FDA*

Felicia Qashu, PhD, *Program Officer, NIH*

Yves Rosenberg, MD, MPH, *Atherothrombosis and Coronary Artery Disease Branch Chief, NHLBI*

Allan Shipp, MHA, *Senior Clinical Research Policy Analyst, Office of Science Policy, NIH*

STAFF

Stacey Adam, PhD, *Scientific Program Manager for Cancer, Foundation for the NIH (FNIH)*
Michael Santos, PhD, *Associate VP of Science, FNIH*
Karen Tountas, PhD, *Scientific Program Manager, FNIH*
David Wholley, MPhil, *Senior VP of Research Partnerships, FNIH*

Rosa Maria Alvarez, PhD*, Consultant, Deloitte*
Helen Q. Chen, PhD, *Senior Consultant, Deloitte*
Benjamin Stratton, PhD, *Senior Consultant, Deloitte*

Lucas Smalldon, MA, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

Timothy Buchman: 07:02

Thank you for emphasizing the importance of "natural history" trials.

Libby Higgs: 58:43

Thanks Ben

Timothy Buchman: 59:09

Thanks to all guests!

High-Level Meeting Summary

Action Items

1. Send Joe and Rosa your preferences for new sub group to join (See table at the end of the document)
2. Review the NCATS Open Data Portal, assess gaps and share recommendations for the in vitro assay inventories

For additional discussion

1. Determine which human samples will be most useful to validating animal models
2. Identify research sites to select for conducting highly specialized analyses such as single cell genomics and proteomics on lung and vascular tissue and blood.
3. Catalogue what actions/resources (e.g., issuing RFPs) are needed to incorporate human tissue analysis into its remit

The Preclinical Working Group (WG) discussed the incorporation of clinical human studies into its objectives and determine what information to include in the NCATS Open Data Portal.

Using Human Data to Advance WG Objectives

The preclinical WG has established a new remit: to analyze human tissue to optimize preclinical animal models and better understand disease biology. The Preclinical WG needs to consider what kinds of human samples and data (and informed consent) will be needed in validating animal models of human COVID-19. As a guiding principle, the collection of human samples should avoid overburdening human participants

To validate animal models for COVID-19, the Preclinical WG has suggested creating a publicly accessible database to share data across studies, and to detail tested compound effects on various human tissues (both adult and pediatric). Preclinical WG will establish criteria for data to be included in this database. By sharing these data, the Preclinical and TX-Clinical WGs can perform consistent decision making in the prioritization process.

Acquisition of Human Molecular Data

The WG needs to identify which samples will be of most value to help fill in the gaps in the research. The WG can then issue requests for proposals (RFPs) on research in those areas.

The WG may (b)(5) [redacted]

(b)(5) [redacted]. The WG (b)(5) [redacted] Drs. (b)(6) [redacted] and (b)(6) [redacted] (b)(5) [redacted]

To conduct COVID-19 compound testing on the largest possible scale, academic laboratories will also need to participate in testing and validation. The WG should coordinate with academic institutions to enlist their help. Although academic institutions may have competing priorities, the ability to use pseudovirus-based assays outside of high containment BSL3/4 facilities may help induce academic laboratories to participate.

The WG will need to further align on a preliminary approach and then seek guidance from ACTIV's Executive Committee to pursue the objectives below:

- Generate a human tissue data inventory
- Fund NPRCs to analyze human tissue
- Identify centralized facilities to conduct highly specialized tissue analysis
- Create RFPs for human tissue analysis
- Entice academic institutions to contribute to this research

The *In Vivo* Strategy Implementation Group of the Preclinical WG will spearhead these efforts to leverage human data to improve animal models.

Incorporation of Additional Data into NCATS Open Data Portal

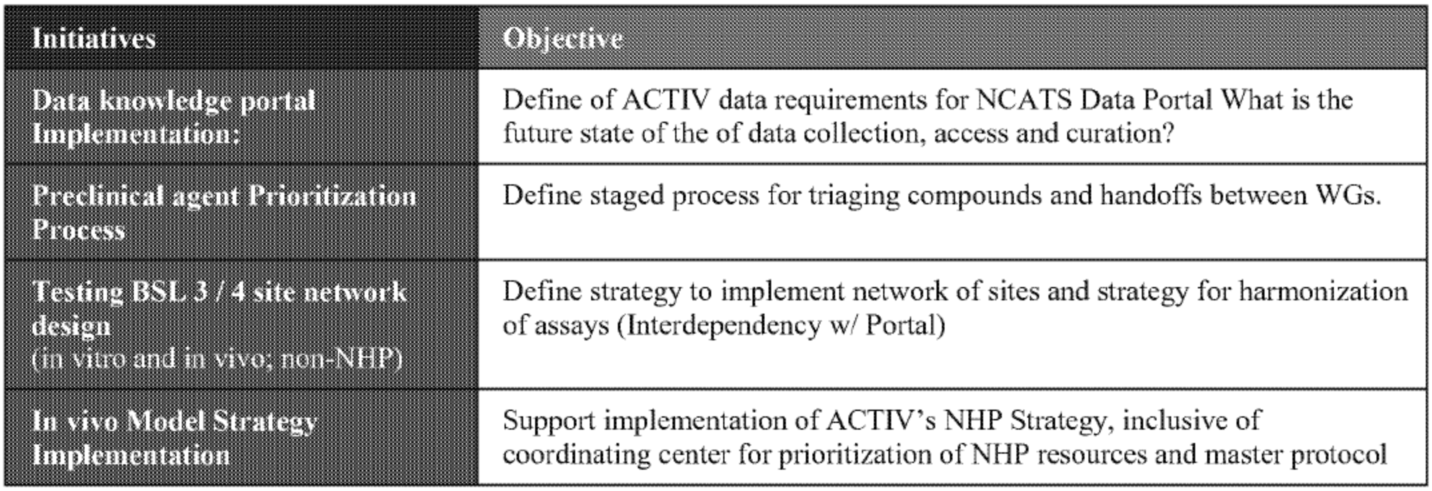
The NCATS Open Data Portal currently consists of NCATS-curated, *in vitro*, high-throughput compound screening data. The Preclinical WG wants to incorporate additional information from investigators testing single compounds *in vitro, in vivo,* or both. The NCATS Portal is well-suited to incorporating *in vitro* data, but the Preclinical WG will need to supplement its structure to support the addition of animal model data. Dr. Greg Gatto provided a template that could be leveraged to define the template for the summaries for animal models Portal. Once modified, Ms. Samantha Jonson will work with NCATS to integrate the animal model data into the NCATS Portal. The detailed animal model data will then be housed at an ACTIV-supported NPRC coordinating center while the NCATS Portal will make publicly available any non-sensitive information. The WG suggested adding a tab or tabs to the portal that lists validated screening assays along with links to model summaries, research site inventories, and the compound prioritization diagram.

Next Steps

The WG will (1) determine which human samples will be most useful to assessing animal models, (2) identify research sites to select for conducting highly specialized analyses, and (3) catalogue what actions/resources (e.g., issuing RFPs) are needed to incorporate human tissue analysis into its remit.

New Preclinical Sub Groups

(slide presented during the meeting)



Initiatives	Objective
Data knowledge portal Implementation:	Define of ACTIV data requirements for NCATS Data Portal What is the future state of the of data collection, access and curation?
Preclinical agent Prioritization Process	Define staged process for triaging compounds and handoffs between WGs.
Testing BSL 3 / 4 site network design (in vitro and in vivo; non-NHP)	Define strategy to implement network of sites and strategy for harmonization of assays (Interdependency w/ Portal)
In vivo Model Strategy Implementation	Support implementation of ACTIV's NHP Strategy, inclusive of coordinating center for prioritization of NHP resources and master protocol

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Peter Adams, PhD, *BARDA*

Annaliesa Anderson, PhD, (not in attendance) *Vice President and CSO Bacterial Vaccines, Pfizer*

Ralph Baric Professor, PhD, (not in attendance) *Dept. of Epidemiology and Dept. of Micobiology and Immunology, UNC Chapel Hill*

Kara Carter, PhD, *Senior Vice President Infectious Disease, Evotec*

Marc Charette, PhD, (not in attendance) *Division of Cardiovascular Diseases NIH, NHLBI*

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Christine Colvis, PhD, *Director, Drug Development Partnership Programs, NCATS*

Damon Deming, PhD, *Virologist, Division of Antiviral Products, Office of New Drugs, FDA*

Michael Diamond, MD, PhD, *Professor, Depts. of Medicine, Molecular Microbiology, Pathology & Immunology, Washington University*

Ken Duncan, PhD, (not in attendance) *Gates Foundation*

Prabhavathi Fernandes, PhD, *Retired, most recently led biotechs Cempra and DarPharma*

Josh Fessel, MD, PhD, (not in attendance) *Division of Lung Diseases NIH, NHLBI*

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Cat Lutz, PhD, (not in attendance) *Senior Director, Mouse Repository & In Vivo Pharmacology, Rare and Orphan Disease Center, Jackson Laboratory*

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Louise Pitt, PhD, *Director, Center for Aerobiological Sciences, USAMRIID*

Tony Punturieri, MD, PhD, (not in attendance) *Division of Lung Diseases NIH, NHLBI*

Srinivas Rao, MBA, PhD, *Global Head Translational In Vivo Models, Sanofi*

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John Young, PhD, *Global Head Infectious Diseases and Vice President, Roche*

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Ashley Parker, PhD, *Health Science Policy Analyst, NIH*
Felicia Qashu, PhD, *Program Officer at National Institutes of Health*

FNIH STAFF
Joseph P. Menetski, PhD, *Associate VP of Research Partnerships, FNIH*
Michael Santos, PhD, *Associate Vice President, Science, FNIH*

Rosa Maria Alvarez, PhD, *Senior Consultant*, *Monitor, Deloitte*

David Frankowski, PhD*, Writer, Rose Li and Associates, Inc*

Appendix B: Chat Transcript

From Alvarez, Rosa Maria to Everyone: 11:51 AM

https://opendata.ncats.nih.gov/covid19/

From Joseph Menetski to Everyone: 11:52 AM

. https://opendata.ncats.nih.gov/covid19/

From Judy Hewitt to Everyone: 12:01 PM

have to go!

High-Level Meeting Summary

The Therapeutics-Clinical Working Group (TX-Clinical WG) discussed this week's SARS-CoV-2 Neutralizing Monoclonal Antibody (mAb) Clinical Summit, and heard updates from its Master Protocol Subgroup (MPSG) on ACTIV's four in-progress master protocols, as well as from its Agent Prioritization Subgroup (APSG) on plans for Wave 2 agent prioritization.

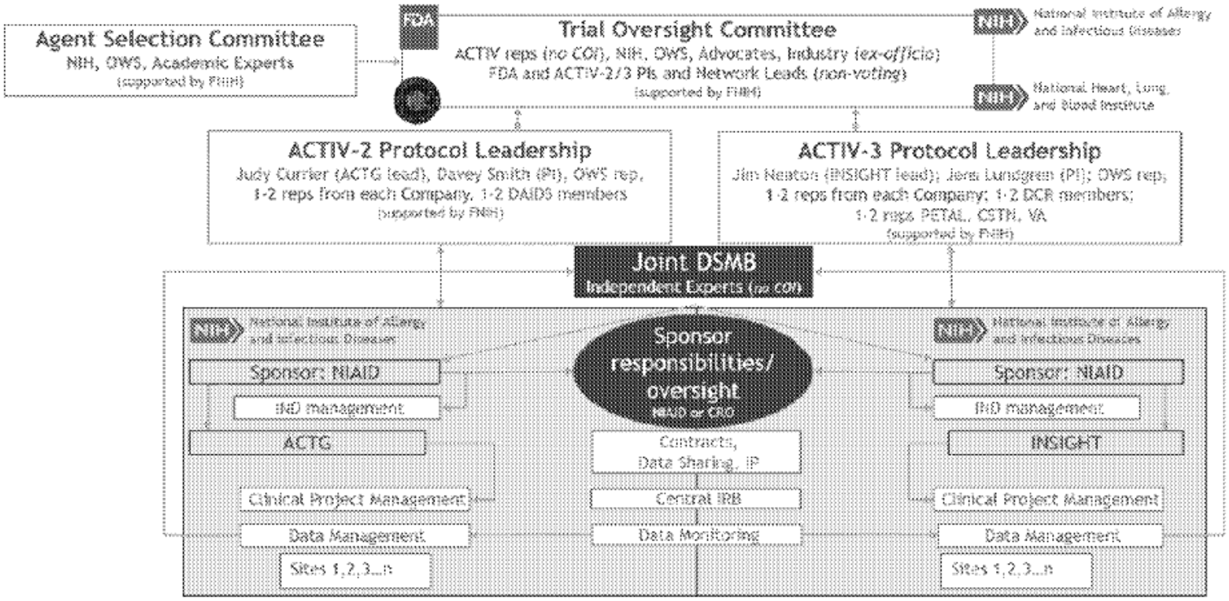
Neutralizing mAb Clinical Summit Updates

In collaboration with Operation Warp Speed (OWS), the TX-Clinical WG facilitated this week's 2-hour Neutralizing mAb Clinical Summit on June 9, 2020 to engage with industry partners on the ACTIV-2 and ACTIV-3 master protocols. During this summit, participants discussed trial governance, entry criteria for ACTIV platform trials, protocol design and strategic rationale, and clinical operations support within USG networks. Each topic above included a question and answer (Q&A) period, and FNIH is now producing a Q&A document for distribution to participants and other stakeholders, including ACTIV members, to capture those portions of the meeting. Participants were also encouraged to submit to FNIH further questions that they would like the Q&A document to address (e.g., given that NIAID will sponsor these trials, how will ACTIV participation affect companies' intellectual property?). FNIH has already distributed a high-level summit summary.

Around 120 attendees participated in the summit, including representatives from approximately fifteen companies; five companies have expressed interest in participating in ACTIV mAb clinical trials as of June 10, 2020. On June 12, the OWS team will begin direct outreach to all companies that attended the summit but have not yet expressed interest in joining ACTIV mAb trials. Dr. Stacey Adam noted that OWS/ACTIV will continue to monitor publicly available information from the approximately thirty additional companies that did not attend the summit but that have SARS-CoV-2 mAbs in early development. OWS will contact these companies when their compounds are closer to ready for testing.

Governance Structure for ACTIV-1 and ACTIV-2

Dr. Adam presented the chart below, which represents the envisioned governance structure for ACTIV-1 and ACTIV-2. The structure is designed to ensure adequate company representation while avoiding any real or perceived conflicts of interest. For example, a Trial Oversight Committee will include ex-officio industry representatives, whereas an Agent Selection Committee will consist entirely of NIH, OWS, and academic experts with no industry representation.


Agent Selection Committee
NIH, OWS, Academic Experts
(supported by FNIH)
FDA
Trial Oversight Committee
ACTIV reps (no COI), NIH, OWS, Advocates, Industry (ex-officio)
FDA and ACTIV-2/3 PIs and Network Leads (non-voting)
(supported by FNIH)
NIH National Institute of Allergy and Infectious Diseases
NIH National Heart, Lung, and Blood Institute
ACTIV-2 Protocol Leadership
Judy Currier (ACTG lead), Davey Smith (PI), OWS rep, 1-2 reps from each Company, 1-2 DAIDS members
(supported by FNIH)
ACTIV-3 Protocol Leadership
Jim Neaton (INSIGHT lead); Jens Lundgren (PI); OWS rep; 1-2 reps from each Company; 1-2 DCR members; 1-2 reps PETAL, CSTN, VA
(supported by FNIH)
Joint DSMB
Independent Experts (no COI)
NIH National Institute of Allergy and Infectious Diseases
Sponsor: NIAID
IND management
ACTG
Clinical Project Management
Data Management
Sites 1,2,3...n
Sponsor responsibilities/ oversight
NIAID or CRO
Contracts, Data Sharing, IP
Central IRB
Data Monitoring
NIH National Institute of Allergy and Infectious Diseases
Sponsor: NIAID
IND management
INSIGHT
Clinical Project Management
Data Management
Sites 1,2,3...n

Discussion

Dr. (b) (6) [redacted] (b) (5) [redacted]. Dr. (b) (6) [redacted] (b) (5) [redacted]

Dr. (b) (6) [redacted] (b) (5) [redacted] Dr. (b) (6) [redacted] (b) (5) [redacted]

Dr. Elizabeth Higgs asked when the MPSG would receive confirmation of specific agents to be tested under ACTIV-1 and ACTIV-2, noting that this information will be crucial to the MPSG's efforts to finalize its trial designs. Dr. Adam stated that the Agent Selection Committee will immediately begin assessing candidate mAbs once it is established, but that exact timelines are unknown.

Dr. Joan Butterton asked what participating companies are expected to contribute to studies aside from their agents. Dr. Adam noted that OWS leadership has decided to require preclinical validation, by independent laboratories, of the neutralizing capacity of each compound prior to entry into ACTIV-1 or ACTIV-2 trials. Therefore, participating companies will each need to sign a Material Transfer Agreement (MTA) and supply sufficient agent to support this validation. Also, because NIAID will sponsor these trials, companies will need to have filed INDs for agents being tested, and these INDs must be open for cross-referencing. Dr. Sarah Read also clarified that the MPSG is still determining who will be responsible for producing clinical study reports.

Dr. Lisa LaVange noted the challenge of sharing trial data through company-specific channels in the context of master protocols testing multiple agents with shared placebo arms. The MPSG is addressing this challenge.

Master Protocol Subgroup Updates

The MPSG presented on the status of its various master protocols now under development:

ACTIV-1
- Inpatient, Phase III Master Protocol
- 3 Host-targeted Immune Modulators
- CRO
- Ready to Launch in June

ACTIV-3
- Inpatient, Phase II/III Master Protocol
- Neutralizing Monoclonal Antibodies
- NIAID INSIGHT + NHLBI PETAL + NHLBI CTSN + VAMC + CRO
- Projected to Launch in July

ACTIV-2
- Outpatient, Phase II/III Master Protocol
- Neutralizing Monoclonal Antibodies
- NIAID ACTG + CRO
- Projected to Launch in July

ACTIV-4
- Inpatient, Phase III Master Protocol
- 2 anticoagulation strategies initially, leading to anticoagulant + anti-platelet, anti-thrombotics combos as indicated
- NHLBI-NINDS "Master" Network
- Projected to Launch in June

ACTIV-1: Immunomodulators (Inpatient Phase III)

The design of ACTIV-1 is nearing completion. In collaboration with Janssen, Bristol Myers Squibb, and AbbVie/Allergan (i.e., the three companies whose immunomodulators are being tested), the MPSG is finalizing its master protocol document. NIAID's Division of Allergy, Immunology, and Transplantation (DAIT) will review the master protocol on June 17, 2020 to decide whether it will sponsor the trial. The ACTIV-1 writing team has also engaged with NCATS' Trial Innovation Network (TIN), which could oversee operational planning and trial implementation. However, a CRO will be needed to run the international component of the trial, as well as to expand the TIN network within the United States. Once it finalizes a sponsor, network, and CRO, the ACTIV-1 writing team will submit its Pre-IND to FDA. ACTIV-1 will likely begin testing during early July.

If DAIT determines that it is unable to sponsor ACTIV-1, the MPSG will solicit the help of a CRO.

ACTIV-2: Monoclonal Antibodies (Outpatient, Phase II/III)

The Pre-IND for ACTIV-2 was submitted to FDA on June 1, 2020; the writing team is anticipating FDA comments by June 17. NIAID's Division of AIDS (DAIDS) is working closely with PPD (a CRO) to coordinate trial implementation. DAIDS is also working closely with (b) (4), the company whose agent will be tested in the first arm of the trial, to ensure agent availability and identify distribution and tracking procedures. Supply orders for non-study product items such as swabs and diagnostics are also in process. Next steps are to receive and respond to FDA's comments on the Pre-IND submission, update the protocol before submitting a new IND to FDA, and define a communications strategy and initiate corresponding public relations campaign to ensure successful trial enrollment.

ACTIV-3: Monoclonal Antibodies (Inpatient, Phase II/III)

The ACTIV-3 writing team submitted its completed master protocol to DAIDS for review by its Clinical Science Review Committee (CSRC), which occurred today. The ACTIV-2 team provided input throughout the writing process to harmonize across ACTIV's inpatient and outpatient mAb trials. The ACTIV-2 and ACTIV-3 writing teams sought to maintain the strengths of each network operationalizing their trials while also ensuring comparability and consistency of data wherever possible across ACTIV-2 and ACTIV-3. The INSIGHT network is working with the ACTIV-3 operations team to delineate the logistical details of protocol implementation, and is working with PETAL, CSTN, and VA teams to determine how best to integrate their sites and catalog capabilities. Together, the INISGHT network and ACTIV-3 operations teams will identify gaps to be filled by a CRO. Next steps are to receive and respond to CSRC comments on ACTIV-3 design and to send FDA a Pre-IND submission on June 15, 2020.

ACTIV-4: Anticoagulants (Inpatient, Phase III)

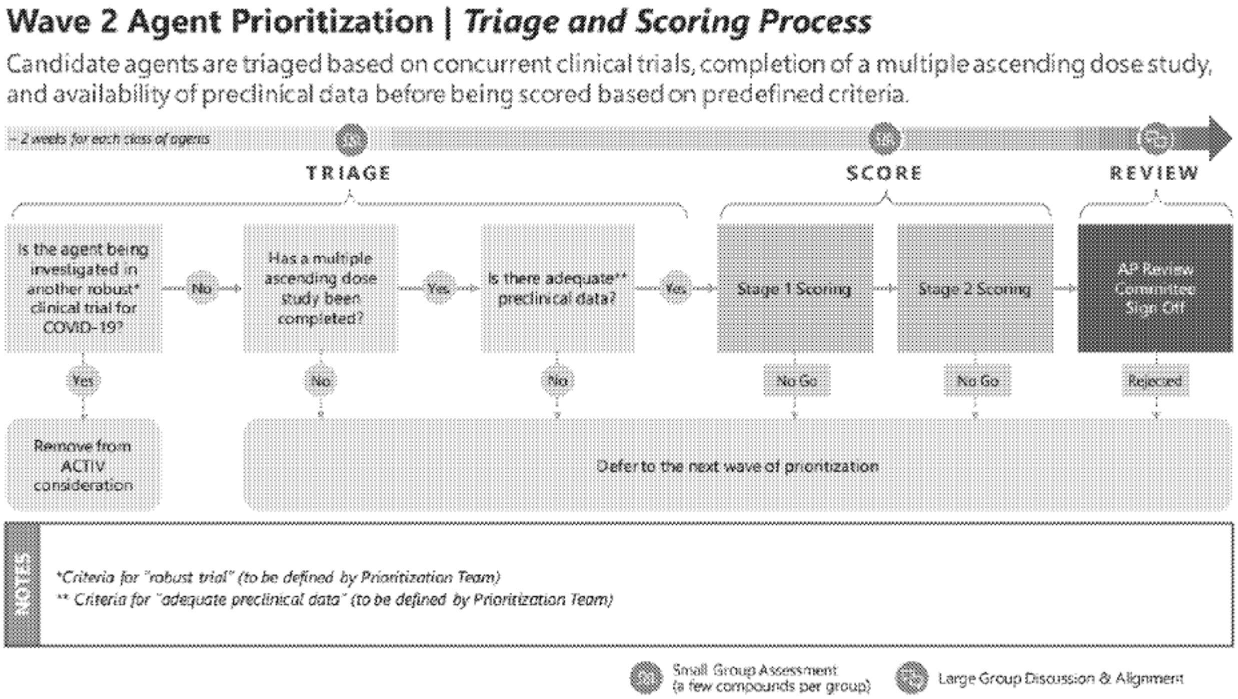
Dr. Andrei Kindzelski provided a brief overview of NHLBI's 'Network of Networks' designed to address COVID-19-related coagulopathies. This network will initially include three studies: (1) in-hospital comparison of low-dose prophylaxis with high-dose treatment; (2) pre-hospital antithrombotic prophylaxis; and (3) post-discharge antithrombotic prophylaxis. The first trial is expected to launch on June 29 or 30. Dr. Adam also noted that the ACTIV-4 team is preparing a more comprehensive update for the TX-Clinical WG next week.

Agent Prioritization Subgroup Updates

The APSG met with Co-Chairs of the TX-Preclinical WG to align on an approach for Wave 2 agent prioritization, with a focus on antivirals. This alignment is necessary because unlike Wave 1 of agent prioritization, Wave 2 will consider agents earlier in the development pipeline, including agents with no existing clinical data, and therefore preclinical validation will be of heightened importance.

The APSG's web-based survey to collect data on candidate agents is live but not on the ACTIV website. The survey link has been shared with members of the TX-Clinical WG and with partnering agencies and investigators who previously contacted ACTIV. Approximately eight submissions have been received so far. Submitters will need approximately 2 to 2.5 hours to complete the survey for any specific compound. Data submitted will remain confidential and will not be entered into the NCATS OpenData Portal.

Four smaller expert teams—focused on antivirals, host-targeted therapies/immunomodulators, symptomatic/supportive therapies, and neutralizing mAbs—will conduct Wave 2 prioritization. An overview of the Wave 2 agent triage and prioritization process is shown below, including the revised agent triage process, which compared to Wave 1 more heavily weighs preclinical data.



Wave 2 Agent Prioritization | *Triage and Scoring Process*

Candidate agents are triaged based on concurrent clinical trials, completion of a multiple ascending dose study, and availability of preclinical data before being scored based on predefined criteria.

~ 2 weeks for each class of agents
TRIAGE
SCORE
REVIEW
Is the agent being investigated in another robust* clinical trial for COVID-19?
No
Has a multiple ascending dose study been completed?
Yes
Is there adequate** preclinical data?
Yes
Stage 1 Scoring
Stage 2 Scoring
AP Review Committee Sign Off
Yes
No
No
No Go
No Go
Rejected
Remove from ACTIV consideration
Defer to the next wave of prioritization
NOTES
Small Group Assessment (a few compounds per group)
Large Group Discussion & Alignment

*Criteria for "robust trial" (to be defined by Prioritization Team)
** Criteria for "adequate preclinical data" (to be defined by Prioritization Team)

Next Steps

The MPSG's ACTIV-2 and ACTIV-3 Subteams will update their protocols based on FDA feedback and then submit their IND applications. The ACTIV-1 writing team will continue to draft its protocol, and the MPSG will continue to collaborate with its selected networks, agencies, and company partners, as well as CROS, to plan for protocol implementation.

The APSG will collect data on potential investigative assets through its web-based survey, and will soon start Wave 2 prioritization for antivirals, host-targeted therapies/immunomodulators, and supportive/symptomatic compounds.

Appendix A: Participants List

WORKING GROUP MEMBERS

Neil Aggarwal, MD, *Lung Biology and Disease Branch Chief, NHLBI*
Sam Bozzette, MD, PhD, *Chief Medical Officer, National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH)*
Timothy G. Buchman, MD, PhD, *Biomedical Advanced Research and Development Authority (BARDA)*
Timothy H. Burgess, MD, MPH, *Captain, Navy, UHSU*
Joan Butterton, MD, *Associate VP, Clinical Research, Infectious Diseases, Merck & Co.*
Judith Currier, MD, *Professor of Medicine in the Division of Infectious Diseases, University of California, Los Angeles (UCLA)*
Ruxandra Draghia-Akli, MD, PhD, *Global Head, Global Public Head R&D, Johnson & Johnson*
Carl Garner, PhD, *VP, Global Regulatory Affairs, Eli Lilly*
Elizabeth (Libby) Higgs, MD, MIA, DTM&H, *Global Health Science Advisor, National Institute of Allergy and Infectious Diseases (NIAID)*
Andrei Kindzelski, MD, PhD, *Program Director, Division of Blood Diseases and Resources, National Heart, Lung, and Blood Institute (NHLBI)*
Walter Koroshetz, MD, *Director, National Institute of Neurological Diseases and Stroke (NINDS)*
Lisa LaVange, PhD, *Associate Chair, Department of Biostatistics, UNC*
John Mellors, MD, *Professor of Medicine, Chief of Infectious Diseases Division, U. Pittsburgh*
Sandeep Menon, PhD, *Senior VP and Head of Early Clinical Development, Pfizer*
Naimish Patel, MD, *Global Development Head of Therapeutic Area, Immunology and Inflammation, Sanofi*
Michael Proschan, PhD, *Mathematical Statistician, Biostatistics Research Branch, NIAID, NIH*
Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH (WG Co-chair)*
Lora Reineck, MD, *Program Director, Lung Biology and Disease Branch, NHLBI*
Yves Rosenberg, MD, MPH, *Atherothrombosis and Coronary Artery Disease Branch Chief, NHLBI*
Peter Stein, MD, *Director of Office of New Drugs, CDER, FDA*

INVITED PARTICIPANTS

Jeremy Brown, PhD, NIH/NINDS
Christine Colvis, PhD, *Director for Drug Development Partnership Programs, NCATS, NIH*
Michelle Culp, MPH, *Office of the Director, NIH*
Ellen Gadbois, PhD, *Office of Science Policy, Office of the Director, NIH*
Mary Groesch, PhD, *NHLBI*
Jacqueline Kirchner, PhD, *Senior Program Officer, Bill and Melinda Gates Foundation*
Hilary D. Marston, MD, MPH, *Medical Officer/Policy Advisor, NIAID, NIH*
Allan Shipp, MHA, *Senior Clinical Research Policy Analyst, Office of Science Policy, NIH*

STAFF

Stacey Adam, PhD, *Director, Cancer, Foundation for the NIH (FNIH)*
Michael Santos, PhD, *Associate VP of Science, FNIH*
Karen Tountas, PhD, *Scientific Program Manager, FNIH*

Rosa Maria Alvarez, PhD*, Consultant, Deloitte*
Helen Q. Chen, PhD, *Senior Consultant, Deloitte*
Benjamin Stratton, PhD, *Senior Consultant, Deloitte*

Lucas Smalldon, MA, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

Timothy Buchman 13:12

(b) (5) [redacted]

Timothy Buchman 19:56

Would you kindly clarify our (this workgroup) role in the agent selection committee?

Koroshetzw 45:29

Lots of cities and States with no PETAL sites. https://petalnet.org/locations

(b) (6) [redacted] **47:03**

(b) (5) [redacted]

Timothy Buchman 47:30

Sort of. Open the "sites" and you will see there are networks beneath. (b) (5) [redacted]

Timothy Buchman 47:55

So the coverage is a little larger than the map shows.

Timothy Buchman 48:27

Here is another example:

Timothy Buchman 48:32

(b) (5) [redacted]

Koroshetzw 49:28

I see. that is wider than I appreciated.

Timothy Buchman 50:10

Yes. And the affiliations are not intuitive, for example:

Timothy Buchman 50:12

(b) (5) [redacted]

(b) (6) [redacted] **54:56**

Thanks Libby. I am also (b) (5) [redacted]

Timothy Buchman 55:19

(b) (5) [redacted]

Timothy Buchman 56:08

(b) (5) [redacted]

Libby Higgs 01:05:53

Sam not sure how to address this issue

High-Level Meeting Summary

The Therapeutics-Clinical (TX-Clinical) Working Group (WG) heard status updates from its Master Protocol Subgroup (MPSG), Agent Prioritization Subgroup (APSG), and TX-Clinical Manuscript Teams, discussed updates related to the upcoming ACTIV pragmatic trial, and heard a presentation on the preliminary findings of the ACTIV-4A trial.

Master Protocol Subgroup Updates

The MPSG reviewed progress on its various master protocols (ACTIV-1/-2/-3/-4/-5).

ACTIV-1: Immunomodulators (Inpatient Phase III)

ACTIV-1 has activated 33 sites (with an additional 4 satellite sites) and (b)(4) The ACTIV-1 team has selected an additional 86 sites (62 U.S. and 24 ex-U.S.) and received regulatory approval to begin activating sites in Argentina, Peru, and Brazil during February.

The team has received FDA comments on the master protocol amendment related to the statistical analysis plan and is currently formalizing their responses. FDA also provided comments related to co-enrollment with ACTIV-4A, which halted enrollment of severe COVID-19 cases after DSMB futility review. The ACTIV-1 DSMB has reviewed data collected from the first 40 patients in each study arm and identified no safety concerns, enabling the studies to proceed as planned.

ACTIV-2: Monoclonal Antibodies (Outpatient, Seamless Phase II/III)

ACTIV-2 has activated 97 sites and (b)(4) patients in total. The ACTIV-2 team has finished enrolling for the (b)(4) open-label arm and activated 40 sites and (b)(4) for the (b)(4) study arm. The team will soon activate Version 3.0 of the master protocol, including agents from (b)(4), and is currently finalizing Versions 4.0 (SAB) and 5.0 ((b)(4)). The team continues to work on ex-U.S. site activation. Dr. Judy Currier requested that the site activation and patient enrollment graphs presented during each TX-Clinical WG meeting be reset upon the start of a new master protocol version.

The team has reviewed externally generated data related to the (b)(4) agent and is now discussing possible placebo groups for infused agents in high risk patient populations; this topic will be discussed during the Cross-Trial Team meeting tomorrow.

Discussion

Dr. Eric Hughes asked whether enrollment has improved since the (b)(4) EUA and publication of positive findings related to mAbs. Dr. Currier noted that the EUA helped ACTIV-2 enroll in certain centers and hopes that these findings and those from ACTIV-2 will advance mAbs as early treatment for COVID-19.

ACTIV-3: Monoclonal Antibodies (Inpatient, Seamless Phase II/III)

ACTIV-3 has activated 38 sites (37 U.S. and 1 in Poland) and (b)(4). The ACTIV-3 team is currently enrolling into Version 2.0 and will soon begin enrolling into Version 3.0.

The team expects its DSMB futility assessment (which required 130 patients per study arm) to occur during the third week of January. The team submitted a pre-IND for the ACTIV-3b study and is assessing whether FDA comments can be returned before the projected date of February 11.

The team has observed some infusion-related patient side effects, including rhabdomyolysis and anaphylaxis. The ACTIV-3 DSMB has reviewed data related to these incidences and deemed the trial safe to proceed.

ACTIV-4: Anticoagulants (Pre-hospitalized/Hospitalized/Post-hospitalized, Phase III)

ACTIV-4's in-hospital protocol (4A) has activated 60 sites and (b) (4) [redacted]. Updates on this trial are included in the summary of Dr. Judith Hochman's presentation (on page 3).

The ACTIV-4 pre-hospitalized protocol (4B) has activated 11 sites and (b) (4) [redacted]. The ACTIV-4B team is finalizing agreements to begin enrolling at CVS MinuteClinics, which will likely begin next week. ACTIV-4B leadership is currently discussing a variety of topics, including whether nurses visiting patients will be vaccinated and whether ACTIV-4 will pay for additional personal protective devices.

The post-hospitalized protocol (4C) will begin enrolling patients next week.

ACTIV-5: Big Effect Trial (Inpatient, Phase II)

ACTIV-5 has activated 11 sites and (b) (4) [redacted]. The ACTIV-5 team continues to identify sites and review additional agents for inclusion into future ACTIV-5 trials.

Pragmatic Trial Update

ACTIV leadership aims to launch a pragmatic trial platform, possibly ACTIV-6, that will definitively evaluate widely available agents with potential therapeutic value for COVID-19, most of which have previously been studied in multiple small-scale trials. The ACTIV pragmatic trial will have clear endpoints, be as remote as possible, and use an updated version of existing agent selection criteria.

Discussion

Dr. Libby Higgs noted that G7 recently convened a meeting of global experts to discuss future pandemic preparedness strategies related to two topics: (1) sharing of reagents to accelerate testing and (2) therapeutic clinical trials. Experts at this meeting emphasized the need for a pragmatic trial platform, similar to that being developed by ACTIV. Mr. David Wholley noted that Dr. Francis Collins has also been meeting with experts to discuss this topic and thus a possible partnership with the UK should be a priority. Dr. Higgs will share with G7 experts that ACTIV is currently developing a pragmatic trial platform and is interested in collaborations.

Agent Prioritization Subgroup Updates

The APSG continues to receive and review 10 to 15 applications per week. Thus far, the APSG has approved 16 agents (three were not advanced because they were being studied in large-scale studies elsewhere), decided to follow-up on 30 agents, deferred 36 agents, and dropped 83 agents.

Manuscript Updates

The TX-Clinical Manuscript Teams received the final round of TX-Clinical WG edits on January 27 and is working to incorporate those edits before submitting the manuscripts to Drs. Collins and Janet Woodcock for final review. Once Drs. Collins and Woodcock's reviews are incorporated into the drafts, the TX-Clinical Manuscript Teams will submit the manuscripts to the *Journal of the American Medical Association* (likely by the end of next week).

ACTIV-4A Progress Update

Overview

Micro- and macro-vascular thrombosis play a prominent role in COVID-19 and lead to elevated d-dimer levels; however, researchers have not reached consensus on how to use d-dimer information to alter clinical decision-making related to anticoagulation strategies. Therapeutic anticoagulation has been shown to correlate with increased survival against COVID-19, but many studies are affected by survivor bias and confounding variables. Thus, ACTIV-4A–a partnership among ACTIV-4; Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP); and Antithrombotic Therapy to Ameliorate Complications of COVID-19 (ATTACC) —was launched to quickly test the hypothesis that anticoagulants will improve clinical outcomes for patients hospitalized with COVID-19.

Study Design

Each of the three partnering trials is a randomized, open-label, adaptive Bayesian trial that uses similar endpoints, protocols, and outcome measures in order to easily combine and evaluate data. The intervention is a therapeutic low molecular weight heparin or unfractionated heparin dosed according to hospital policy for venous thrombotic events (VTEs) and the control arm is standard prophylactic care. Patients were treated for 14 days or until discharged from the hospital. The primary outcome is organ support-free days (OSFDs), which combines information from ordinal scales and mortality; organ support is defined by requiring ICU-level care (e.g., mechanical ventilation, vasopressors, or high-flow oxygen; high-flow oxygen requirements were defined as 20 to 30 liters). The secondary outcomes for safety are major hemorrhage and heparin-induced thrombocytopenia (HIT) and for efficacy are mortality, intubation, major thrombosis, pulmonary embolism, VTE, stroke, myocardial infarction, and length of stay. Analyses are stratified by COVID-19 severity (i.e., moderate defined as hospitalized but not requiring ICU level of care, and severe defined by requiring ICU level of care and organ support) as well as by d-dimer level (i.e., high, low, or unknown). Adaptive design decision rules declared superiority if findings showed a 99 percent probability of superiority on primary outcome and declared futility if the findings displayed a less than 5 percent probability of at least 20 percent improvement for primary outcome. The study team will also evaluate outcomes for each d-dimer stratum.

Preliminary Results and DSMB Futility Assessment

In total, ACTIV-4A, REMAP-CAP, and ATTACC randomized a total of 2,895 patients, approximately 2,293 of which had OSFDs (1,398 moderate and 985 severe patients); the overall patient population had an average age of 60 and included slightly more males than females. During a December 2020 futility assessment, DSMBs from the three ACTIV-4A partners recommended discontinuing enrollment of severe state patients for futility (follow-up with already enrolled severe patients will continue, as stated in the protocol). DSMBs also recommended discontinuing enrollment of moderate state patients for superiority in both d-dimer strata, noting that the safety profile supports therapeutic benefit of anticoagulation in moderate state patients.

For the primary outcome of OSFDs, both the high and low d-dimer moderate patient groups displayed a 99 percent superiority probability; however, the severe state group displayed a 98 percent probability of inferiority. Further analyses found that each moderate patient d-dimer stratum displayed reduced mortality and requirements for organ support when given therapeutic anticoagulant, compared to prophylactic doses of anticoagulant. However, severe patients did not display these benefits and instead displayed increased mortality.

Approximately 1.6 percent of moderate patients and 3.7 percent of severe patients receiving therapeutic anticoagulant displayed major bleeding; however, these results are preliminary, unadjudicated, and potentially subject to reporting bias. In addition, both moderate and severe patients receiving therapeutic anticoagulant displayed fewer thrombotic events, than those receiving prophylactic anticoagulant doses; however, these results may be impacted by increased mortality and organ support requirements in the severe patient group.

Interim Conclusions

Preliminary analyses suggest that the therapeutic dose of anticoagulant provides superior benefit to moderate state patients who are hospitalized but do not require organ support care. However, severe state patients requiring ICU-level organ support do not improve with the therapeutic anticoagulant dose and may instead be harmed by it. The ACTIV-4A team is now discussing how the results of this study can be applied to clinical decision making for moderate patients who become critically ill during hospitalization.

Discussion

Participants thanked Dr. Hochman for an insightful presentation. Dr. Timothy Buchman suggested mentioning in future presentations that patients are administered therapeutic doses of anticoagulant even when thrombotic events occur. Dr. Hochman noted that this continued administration is a study protocol requirement.

Consistency of Findings across ACTIV-4A Trials

Dr. Hochman noted that certain patient populations were predominantly enrolled in different trials, which may cause minute differences in analytical results (particularly for the severe state group). For example, REMAP-CAP initially enrolled only ICU-level patients and ATTACC initially enrolled only non-ICU level patients. As a result, most severe state patients were enrolled via REMAP-CAP and moderate state patients enrolled via ATTACC and ACTIV-4. Analyses for the moderate state patient group were consistent across the three trials. However, the severe patient populations enrolled across the three trials were slightly different and these differences will likely impact individual trial results. These observations led the ACTIV-4A team to discuss whether certain severe state patient populations, particularly the high-flow oxygen group, may behave differently than other severe state groups and instead act more like moderate patients.

Promising Biomarkers

Dr. Hochman noted that ACTIV-4A evaluated multiple biomarkers, including CRP, d-dimer, troponin, and calcitonin, but did not observe any promising trends. Most ICU-level patients display elevated d-dimer levels, suggesting a connection between d-dimer and the degree of ICU-level support required; however, these hypotheses require further investigation.

Sensitivity Analyses

Dr. Hochman noted that sensitivity analyses were completed for mortality data using a neutral prior distribution. She invited Dr. Michael Proschan to contact members of the ACTIV-4A statistician team (including Drs. Maria Brooks and Eric Leifer) to discuss these analyses further.

Appendix A: Participants List

WORKING GROUP MEMBERS

Neil Aggarwal, MD, *Lung Biology and Disease Branch Chief, National Heart, Lung, and Blood Institute (NHLBI)*

Timothy G. Buchman, MD, PhD, *Biomedical Advanced Research and Development Authority*

Joan Butterton, MD, *Associate VP, Clinical Research, Infectious Diseases, Merck & Co.*

Judith Currier, MD, *Professor of Medicine in the Division of Infectious Diseases, University of California, Los Angeles*

R. Angelo DeClaro, MD, *Division Director (Acting), Division of Hematologic Malignancies, Food and Drug Administration (FDA)*

Ruxandra Draghia-Akli, MD, PhD, *Global Head, Global Public Head R&D, Johnson & Johnson*

Elizabeth (Libby) Higgs, MD, MIA, DTM&H, *Global Health Science Advisor, National Institute of Allergy and Infectious Diseases (NIAID)*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis (WG Co-chair)*

Andrei Kindzelski, MD, PhD, *Program Director, Division of Blood Diseases and Resources, NHLBI*

Lisa LaVange, PhD, *Professor and Associate Chair, Department of Biostatistics, UNC Chapel Hill*

Elliott Levy, MD, *Senior VP Global Development, Amgen; TransCelerate Board Member*

John Mellors, MD, *Professor of Medicine, Chief of Infectious Diseases Division, University of Pittsburgh*

Michael Proschan, PhD, *Mathematical Statistician, Biostatistics Research Branch, National Institute of Allergy and Infectious Diseases (NIAID), NIH*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID (WG Co-chair)*

Yves Rosenberg, MD, MPH, *Atherothrombosis and Coronary Artery Disease Branch Chief, NHLBI*

Larry Tsai, MD, *Global Head of Respiratory and Rheumatology Product Development, Genentech*

INVITED PARTICIPANTS

Timothy H. Burgess, MD, MPH, *Captain, Navy*

Christine Colvis, PhD, *Director, Drug Development Partnership Programs, NCATS*

Michelle Culp, MPH, *Office of the Director, NIH*

Ellen Gadbois, *Program Lead, Emerging Biotechnology Policy, NIH Office of Science Policy*

Judith Hochman, MD, *Co-Director of the Clinical and Translational Science Institute and Associate Director of Cardiology, NYU Langone Health*

Jacqueline Kirchner, PhD, *Senior Program Officer, Bill and Melinda Gates Foundation*

Andrea Lerner, MD, MS, *Medical Officer, Office of the Chief of Staff, NIAID*

Joanne Lumsden, PhD, *NCATS*

Robert Malone, MD, *Chief Medical Officer, Alchem Laboratories Corporation*

Ashley Parker, PhD, *Health Science Policy Analyst, NIH*

Martha Petrovick, *MIT Lincoln Laboratory*

Revell Phillips, PhD, *Science and Technology Manager, Defense Threat Reduction Agency*
Ronald Reisler, MD, MPH, *Senior Clinical Advisor, Davis Defense Group*
Daniel Rubin, PhD, *Statistician, Center for Drug Evaluation and Research, FDA*
Christine Sizemore, PhD, *Director, Division of International Relations, Fogarty International Center, NIH*

STAFF
Stacey Adam, PhD, *Director, Cancer, Foundation for the NIH (FNIH)*
David Wholley, MPhil, *Senior Vice President of Research Partnerships, FNIH*

Helen Chen, PhD, *Consultant, Deloitte*
Evan Appell, *Consultant, Deloitte*
Hana Nasr, MPH, *Consultant, Deloitte*
Alex Sorosa, *Business Analyst, Deloitte*

Bethany Stokes, MS, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

From Timothy Buchman to Everyone: 01:20 PM

Wearing my editor had, I just received a lookback study or(b)(5) in COVID.

From Libby Higgs to Everyone: 01:20 PM

I met (as part of USG group in prep for G7) with UK trial leadership today and there may be interest in collaboration.

From Timothy Buchman to Everyone: 01:20 PM

Colchicine is in the news today.

From Timothy Buchman to Everyone: 01:26 PM

Are you planning a paired submission?

From Libby Higgs to Everyone: 01:41 PM

What was classified as a major bleed?

From Eric Hughes to Everyone: 01:44 PM

Great work! Thank you!

From Judith Currier to Everyone: 01:44 PM

Great work and such important data for the field.

From Timothy Buchman to Everyone: 01:55 PM

Once again BRAVO!

High-Level Meeting Summary

The Therapeutics-Clinical (TX-Clinical) Working Group (WG) heard status updates from its Master Protocol Subgroup (MPSG) and a presentation on the efforts of the Preclinical Therapeutics WG's Emerging Viral Sequencing Subgroup.

Master Protocol Subgroup Updates

The MPSG reviewed progress on its various master protocols (ACTIV-1/-2/-3/-4/-5).

ACTIV-1: Immunomodulators (Inpatient Phase III)

ACTIV-1 has activated 30 sites and (b)(4). The ACTIV-1 team has selected an additional 83 sites (60 U.S. and 23 ex-U.S.) and received regulatory approval to begin activating sites in Argentina and Peru, with approval expected soon from Mexico and Brazil. The team aims to increase enrollment of Hispanic/Latinx patients through collaborations with the ACTIV Communications Team.

The team received IRB approval of the master protocol amendment and has received two sets of FDA comments related to the amendment's detailed plans for statistical analyses and co-enrollment with other master protocols. ACTIV-1 statisticians are now evaluating the comments related to the statistical analysis plan and the team has resolved issues related to co-enrollment. The ACTIV-1 DSMB has reviewed data collected from the first 40 patients in each study arm and identified no safety concerns, enabling the studies to proceed as planned.

The ACTIV Cross-Trial Operations team has provided feedback to aid the ACTIV-1 team in resolving site issues related to some challenges with some of the contracting language for their sites.

ACTIV-2: Monoclonal Antibodies (Outpatient, Seamless Phase II/III)

ACTIV-2 has activated 95 sites and (b)(4) within the (b)(4) study arm. It has activated 24 sites and (b)(4) within the (b)(4) study arm. The ACTIV-2 team continues to work with Black-led organizations to improve enrollment of African American patients. The team has received approval to begin activating sites in South Africa and expects to receive approval in other countries soon.

The team has received safe-to-proceed approval from FDA on Version 3.0 of the master protocol, which includes agents from (b)(4), and is working to submit Version 4.0 of the master protocol to the FDA during January. The team is also developing Version 5.0 of the master protocol, which will likely include the (b)(4) agent. The team has begun analyzing data from the (b)(4) study arm, particularly to investigate the relationship between COVID-19 symptoms and virology.

ACTIV-3: Monoclonal Antibodies (Inpatient, Seamless Phase II/III)

ACTIV-3 has activated 34 sites and (b)(4) into each of the Version 2.0 master protocol arms (i.e., (b)(4)) and will meet with the ACTIV-3 DSMB on January 25 to discuss data from these patients. The ACTIV-3 team will soon begin enrolling patients into Version 3.0 of the master protocol, which includes the (b) (4) agent. The team is now in discussions with (b) (4) to include its agent within Version 4.0 of the master protocol. The team has developed a protocol for the ACTIV-3B (b) (4) and (b) (4) factorial study and submitted it to NIAID for review. In addition, the ACTIV-3 hyper-immunoglobulin study has (b) (4) and will likely soon complete enrollment.

ACTIV-3 has activated one site in Poland; however, the team has experienced challenges in activating ex-U.S. sites because many countries wish to review more data before approving trials. The team hopes that data resulting from the second DSMB review will be sufficient to achieve approval in more countries. Further, the team has observed that certain U.S. ACTIV-3 sites perform significantly better than others in terms of patient enrollment, particularly sites at Baylor Scott & White Health and Duke University Hospital.

Discussion

Dr. Revell Philips suggested that the ACTIV-3 team capture lessons learned and patient enrollment strategies from the high-performing ACTIV-3 sites in order to provide guidance to other ACTIV trials, as well as the clinical trial community overall. This goal is of interest to ACTIV leadership, as well, as Dr. Stacey Adam noted. Dr. Libby Higgs noted that the Duke University Hospital site has collected some of this information (e.g., reasons why a patient refused consent) and shared it with other ACTIV-3 investigators; the Duke University Hospital also successfully used the informational flipbook and graphics resources in order to enhance patient enrollment. The Baylor Scott & White and Duke University Hospital sites are CTSN sites with previous experience in cardiothoracic clinical trials experience; Dr. Judith Currier noted that this fact may suggest that sites with existing infrastructure and relevant experience are likely to perform better.

Dr. Timothy Buchman recommended contacting more senior executives within each ACTIV-3 site in order to bolster patient enrollment in low-performing sites. All academic sites are hierarchical in nature and a top-down approach to enhancing enrollment may be helpful.

ACTIV-4: Anticoagulants (Pre-hospitalized/Hospitalized/Post-hospitalized, Phase III)

ACTIV-4's in-hospital protocol (4A) has activated 58 sites and (b) (4) . ACTIV-4A has partnered with the Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) and Antithrombotic Therapy to Ameliorate Complications of COVID-19 (ATTACC) Trials. ACTIV-4A, REMAP-CAP and ATTACC held the first combined DSMB meeting, which included DSMBs from each trial partner. During this meeting, DSMB officials upheld the need to discontinue enrolling patients requiring ICU-level care into the three studies' therapeutic/anti-coagulant study arms; additional results of this meeting will be announced today.

The ACTIV-4 pre-hospitalized protocol (4B) has activated 11 sites and (b) (4) . With the help of the CONNECTS Network, the ACTIV-4B team aims to soon finalize an agreement with CVS to leverage MinuteClinic locations for patient enrollment.

The post-hospitalized protocol (4C) will launch during January. The ACTIV-4C team is finalizing agreements and is beginning to select sites. In addition, the team aims to leverage ACTIV-4A sites in order to transition patients from the in-hospital arm into this arm.

Discussion

Dr. Buchman asked whether the data that resulted in the DSMB's decision to halt ICU-level patient enrollment will be made public in order to shape guidelines currently in development. Dr. Andrei Kindzelski noted that these data were not generated through ACTIV-4A, but through the REMAP-CAP and ATTACC studies; ACTIV-4A does not yet have a sufficient sample size to draw such conclusions. REMAP-CAP and ATTACC will soon publish data in a joint publication, which is expected within the next week.

ACTIV-5: Big Effect Trial (Inpatient, Phase II)

ACTIV-5 has activated nine sites and (b)(4) [redacted]. The ACTIV-5 team continues to identify sites and review additional agents for inclusion into future ACTIV-5 trials.

Preclinical Emerging Viral Sequence Data Collection

Dr. Joseph P. Menetski, FNIH

ACTIV leadership asked the Preclinical WG to develop efforts to evaluate viral resistance in response to the identification of new variants around the globe and the observation that individuals were becoming re-infected with new variants after contact with a mink farm in Denmark. The Preclinical WG thus launched the Emerging Viral Sequencing Subgroup, with members from government, industry, academia, and non-profits, to define the preferred framework and scope of this effort; to date, many companies have been sequencing viral variants on a small scale, but these efforts have not been coordinated. The Emerging Viral Sequencing Subgroup also began convening representatives from various industry representatives to discuss methods to share relevant data with companies participating in ACTIV master protocols. The Subgroup then submitted a proposal to Dr. (b)(6) [redacted] and was (b)(5) [redacted]

To complete its remit, the Subgroup will coordinate variant data from companies and literature in order to evaluate these variants according to their effect on therapeutic efficacy in order to enhance medical decision making. The currently proposed Subgroup workflow includes five steps, shown below:

1. Monitor global emergence and circulation of SARS-CoV-2 mutations
2. Cross-reference variants against database of experimentally/clinically phenotyped mutants
3. Characterize variants via in vitro critical-path assays
4. Characterize variants via in vivo critical-path assays
5. Rapidly share results with the scientific community

To support this workflow, the Emerging Viral Sequencing Subgroup will create five Subteams to address five related aims: (1) establish criteria for prioritizing emerging variants, (2) identify critical assays to be done sequentially or in parallel, (3) provide guidance for producing high-quality reference materials, including viral isolates and both convalescent and post-vaccination plasma samples, (4) outline a rapid and high-quality deep sequencing pipeline for variant confirmation, and (5) share phenotypic and sequence data from industry partners.

Further, the Emerging Viral Sequencing Subgroup also aims to synergize its efforts with the governmental SARS-CoV-2 Interagency Group (SIG), which is a partnership among NIAID, BARDA, and CDC. The Subgroup believes it can support SIG by providing additional in vitro and in vivo variant data, tools, and other data resources and will continue to coordinate efforts with SIG as ACTIV's efforts progress.

Discussion

Dr. Philips asked whether SIG has considered incorporating representation from DOD's Global Emerging Infections Surveillance program. Dr. Menetski recommended that Dr. Phillips discuss DOD representation in SIG with Dr. Emily Erbelding and noted that this expertise would also be welcome within the Emerging Viral Sequencing Subgroup. Dr. Menetski noted that the Broad Institute is not currently involved in the Emerging Viral Sequencing Subgroup's efforts, in response to a question from Dr. Eric Hughes in the chat box.

Dr. John Mellors suggested that the Emerging Viral Sequencing Subgroup (1) assess variants in patients who display vaccine breakthrough and have neutralizing antibodies and (2) evaluate baseline SARS-CoV-2 genotype in relation to virologic response during mAb treatment. Dr. Jacqueline Kirchner agreed with Dr. Mellors' suggestion and added that evaluating the relationship between variants and mAb treatment may be difficult if variants are not emerging in regions where mAb treatment is more prevalent; in addition, she recommended the Subgroup also consider evaluating variants using in vitro neutralization assays with live virus and pseudovirus.

Dr. Currier recommended coordinating the efforts of ACTIV-2's viral sequencing project with the Emerging Viral Sequencing Subgroup. Dr. Menetski agreed with Dr. Currier's recommendation and added that the Subgroup hopes to develop a database to enable easy sharing of viral sequencing data. Dr. Mellors recommended using Stanford University's HIV Drug Resistance Database as the template for the ACTIV database. Dr. Buchman offered to develop a novel publication type that would grant researchers who upload data to the ACTIV database academic credit; he and Dr. Menetski will discuss this topic further offline.

Appendix A: Participants List

WORKING GROUP MEMBERS

Neil Aggarwal, MD, *Lung Biology and Disease Branch Chief, National Heart, Lung, and Blood Institute (NHLBI)*

Timothy G. Buchman, MD, PhD, *Biomedical Advanced Research and Development Authority*

Joan Butterton, MD, *VP, Clinical Research, Infectious Diseases, Merck & Co.*

Judith Currier, MD, *Professor of Medicine in the Division of Infectious Diseases, University of California, Los Angeles*

Ruxandra Draghia-Akli, MD, PhD, *Global Head, Global Public Head R&D, Johnson & Johnson*

Keith Gottesdiener, MD, *Former President and Chief Executive Officer, Rhythm*

Elizabeth (Libby) Higgs, MD, MIA, DTM&H, *Global Health Science Advisor, National Institute of Allergy and Infectious Diseases (NIAID)*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis (WG Co-chair)*

Andrei Kindzelski, MD, PhD, *Program Director, Division of Blood Diseases and Resources, NHLBI*

Jacqueline Kirchner, PhD, *Senior Program Officer, Bill and Melinda Gates Foundation*

Elliott Levy, MD, *Senior VP Global Development, Amgen; TransCelerate Board Member*

John Mellors, MD, *Professor of Medicine, Chief of Infectious Diseases Division, University of Pittsburgh*

Michael Proschan, PhD, *Mathematical Statistician, Biostatistics Research Branch, National Institute of Allergy and Infectious Diseases (NIAID), NIH*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID (WG Co-chair)*

Yves Rosenberg, MD, MPH, *Atherothrombosis and Coronary Artery Disease Branch Chief, NHLBI*

INVITED PARTICIPANTS

Christine Colvis, PhD, *Director, Drug Development Partnership Programs, NCATS*

Ellen Gadbois, *Program Lead, Emerging Biotechnology Policy, NIH Office of Science Policy*

Peter Kim, MD, *Director, Therapeutics Research Program, Division of AIDS, NIAID, NIH*

Andrea Lerner, MD, MS, *Medical Officer, Office of the Chief of Staff, NIAID*

Joanne Lumsden, PhD, *NCATS*

Robert Malone, MD, *Chief Medical Officer, Alchem Laboratories Corporation*

Ashley Parker, PhD, *Health Science Policy Analyst, NIH*

Martha Petrovick, *MIT Lincoln Laboratory*

Revell Phillips, PhD, *Science and Technology Manager, Defense Threat Reduction Agency*

Dionne Price, PhD, *Office of Biostatistics of the Center for Drug Evaluation and Research, FDA*

Lora Reineck, MD, *Program Director, Lung Biology and Disease Branch, NHLBI*

Ronald Reisler, MD, MPH, *Senior Clinical Advisor, Davis Defense Group*

Daniel Rubin, PhD, *Statistician, Center for Drug Evaluation and Research, FDA*

STAFF

Stacey Adam, PhD, *Director, Cancer, Foundation for the NIH (FNIH)*
Joseph P. Menetski, PhD, *Associate VP, Research Partnerships, FNIH*
David Wholley, MPhil, *Senior Vice President of Research Partnerships, FNIH*

Helen Chen, PhD, *Consultant, Deloitte*
Evan Appell, *Consultant, Deloitte*
Harrison Hawk, *Consultant, Deloitte*
Hana Nasr, MPH, *Consultant, Deloitte*
Alex Sorosa, *Business Analyst, Deloitte*

Bethany Stokes, MS, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

From Libby Higgs to Everyone: 01:08 PM

Judy, Impressive total enrollment. Completely agree international reg issues are challenging.

From Eric Hughes to Everyone: 01:08 PM

👍💪

From Timothy Buchman to Everyone: 01:09 PM

Amazing progress. Congratulations, Judy!

From Currier, Judith, M.D. to Everyone: 01:10 PM

thanks!

From Eric Hughes to Everyone: 01:13 PM

go Duke and Baylor!💪

From Revell Phillips to Everyone: 01:14 PM

Any way to capture some lessons learned from the high enrolling sites, and share those techniques with the other sites?

From Timothy Buchman to Everyone: 01:17 PM

This is so important! Thanks Libby

We surgeons start earlier than 0500--we are at the hospital by that time!@

From Eric Hughes to Everyone: 01:40 PM

is the Broad Institute in Boston involved?

From Revell Phillips to Everyone: 01:45 PM

Does DoD have a seat?

From Libby Higgs to Everyone: 01:46 PM

Helpful Joe to understand how the SIG group fits in to ACTIV

From Robert Malone to Everyone: 01:52 PM

I am not aware of any validated correlate of protection, nor associated validated assays designed to assess such a correlate. Does one exist?
Lots of assumptions being made about what various investigator groups consider assays of "neutralizing antibodies", but I am not aware of any of those meeting rigorous criteria as measuring a correlate of vaccine- or viral infection-induced protection

From Eric Hughes to Everyone: 01:58 PM

great start!

High-Level Meeting Summary

Action Items

- WG members are requested to review the slide outlining expected NHP needs and provide feedback.
- Continue to generate data dictionary for animal model inventory

Points for additional discussion:

- Where would the animal model data be stored, FNIH, Tulane NPRC, other?
- liaise with NCATS to determine how to streamline the inventory integration process
- Owners of active maintenance of the animal model inventory in the short-term vs. long-term

Summary

The ACTIV preclinical working group (WG) met to review updates to the animal model inventory and how to allocate nonhuman primates (NHPs) to COVID-19 treatment studies.

Animal Model Inventory Updates

Dr. Judy Hewitt shared the current animal model inventory, which summarizes promising small animal and non-human primate (NHP) models that may be used to identify treatment compounds for COVID-19. The inventory was initially created as an Excel spreadsheet by members of the WG and incorporated input from the ACTIV Clinical Therapeutics and Vaccines WGs. Individuals at NCATS are now transforming this spreadsheet into a REDCap form that will automatically populate a repository of animal models. Several problems with the REDCap survey, such as the inability to update previous entries, are being addressed by the NCATS IT support team. In addition, Dr. Hewitt, Dr. Cat Lutz, and Dr. Clint Florence are generating a 'data dictionary' that defines the terms researchers can enter into the database to ensure uniform usage; words such as 'source', 'vendor', and 'background' have thus far been used inconsistently during data entry.

As the animal model inventory grows, it will likely include proprietary and otherwise sensitive information. Discussants agreed that some information should be reserved for private dissemination and that determinations of public and private data should apply typical manuscript publication criteria; any data that may be published in an academic journal will be shared publicly (which includes the handling of intellectual property, typically outlined in patent agreements), whereas detailed sensitive data may be shared only at specific permission levels granted individually.

The logistics of data storage will affect the ability to keep data confidential. NCATS is subject to the Freedom of Information Act (FOIA), which would allow the public to request data that may include private information. (b)(5) [redacted]

The animal model inventory is nearly complete and will need to be housed in a freestanding location and made accessible to the research community until it is incorporated into the NCATS Open Data Portal, which has yet to be launched. Ms. Samantha Jonson will liaise with NCATS to determine how to streamline the inventory integration process. The animal model inventory will also require active maintenance throughout the COVID-19 pandemic. ACTIV staff will be selected to curate the continuous influx of animal model data and determine, based on the extent of validation, when model information becomes redundant.

Discuss NHP Staged Validation Process

ACTIV leadership will need to know how many NHPs (and what species) are needed for the next year to be used in the master NHP protocols it is developing for testing COVID-19 therapeutics, neutralizing antibodies, and vaccines. Dr. Joseph Menetski shared a slide that showed an estimated need for 140-260 African green monkeys (AGMs) and 200-452 rhesus macaque monkeys to enable the clinical testing of 20-30 therapeutics (half of which would be antivirals tested in small animals), 20-30 neutralizing compounds, and 15-20 vaccines in the next year. The slide further outlined how, and how many of, these monkeys would be used per protocol group. Dr. Rappaport noted that, because of the limitation in number of NHPs (particularly AGMs), only 20 AGMs and 20 macaques (total) will be used for validation studies. However, many validation studies have already been completed in macaques to provide confidence in this model. AGMs will need to be imported from the Caribbean to the United States (or elsewhere) in the coming year, especially if older monkeys are needed to approximate the human symptoms of COVID-19 (e.g., inducing a cytokine storm and ARDS).

The WG plans to use its NHP prioritization framework for one year and acknowledges that the plan reflects a 'crisis mode' during the pandemic and not the typical allocation of resources outside a pandemic environment. NHP prioritization will continue for the year, independent of future compound successes, for several reasons: (1) preclinical successes may fail in the clinic, (2) a compound's success may be found only for a specific stage of the disease (e.g., mild vs. moderate vs. critical illness stages), and (3) treating COVID-19 as a whole will require treatments from each group of master protocols. However, while the overall prioritization framework will remain in place, future successes may shape WG priorities to evolve with the virus and the compounds that treat it. WG members may also need to outline the data necessary to validate potential future NHP models.

Next Steps

Ms. Jonson will work with NCATS to determine how to integrate the WG animal model inventory with the Open Data Portal and Dr. Rappaport will coordinate with the WG to store the animal model inventory at the Tulane University NPRC database. In addition, WG members are requested to review the slide outlining expected NHP needs and provide feedback.

Appendix A: Participants List

WORKING GROUP MEMBERS

Annaliesa Anderson, PhD, *Vice President and CSO Bacterial Vaccines, Pfizer*
Ralph Baric, PhD, *Professor, Dept. of Epidemiology and Dept. of Microbiology and Immunology, UNC Chapel Hill*
Tomas Cihlar, PhD, *Vice President of Virology at Gilead Sciences*
Christine Colvis, PhD, *Director, Drug Development Partnership Programs, NCATS*
Damon Deming, PhD, *Virologist, Division of Antiviral Products, Office of New Drugs, FDA, CDER, DAV*
Michael Diamond, MD, PhD, *Professor, Depts. of Medicine, Molecular Microbiology, Pathology & Immunology, Washington University School of Medicine*
Prabhavathi Fernandes, PhD, *Retired*
Nancy Haigwood, PhD, *Director, Oregon National Primate Research Center, OHSU*
Clint Florence, PhD, *Program Officer, Research Resource Section, OBRR, DMID, National Institute of Allergy and Infectious Diseases (NIAID)*
Greg Gatto, PhD, *Drug Development Regulatory Project Leader at RTI*
Jay Grobler, PhD, *Executive Director, Infectious Disease and Vaccines Discovery, Preclinical, and Early Development (DPED), Merck Research Laboratories*
Judy Hewitt, PhD, *Deputy Director, Office of Biodefense, Research Resources and Translational Research New Drugs, NIAID*
Samantha Jonson, MPS, *Special Assistant to the Director, NCATS*
Elizabeth Ottinger, PhD, *Project Manager, NCATS*
David Payne, PhD, DSc, *Vice President & Head, Medicine Opportunities Research Unit, GlaxoSmithKline*
M. Louise M. Pitt, PhD, *Science Advisor – USAMRIID / DoD*
Srinivas Rao, MBA, PhD Global Head, Translational In Vivo Models Global Research Platform, Sanofi.
Jay Rappaport, PhD, *Director and Chief Academic Officer at Tulane Primate Center*
John Young, PhD, *Global Head Infectious Diseases and Early Development, Roche*

INVITED PARTICIPANTS

Ken Duncan, PhD, *Deputy Director, Discovery: Therapeutics, Bill and Melinda Gates Foundation*
Ashley Parker, PhD, *Health Science Policy Analyst, NIH*
Felicia Qashu, PhD, *Program Officer at National Institutes of Health*

FNIH STAFF

Joseph P. Menetski, PhD, *Associate VP of Research Partnerships, FNIH*

Rosa Alvarez, PhD, *Senior Consultant*, *Monitor, Deloitte*
Benjamin Stratton, *Senior Consultant, Deloitte*

David Frankowski, PhD, *Writer, Rose Li and Associates, Inc*

Appendix B: Chat Transcript

From Liz Ottinger to Everyone: 10:32 AM

Sorry, my internet connection is unstable and I keep losing connection-Liz

From Writer: Dave Frankowski to Everyone: 10:38 AM

You're at NHP staged validation

From Jay Grobler to Everyone: 11:01 AM

I have a hard stop and have to run. Bye everyone.

From Michael Diamond to Everyone: 11:02 AM

I have a car stop as well

hard stop

From Srinivas Rao to Everyone: 11:02 AM

I have to go as well. thanks all.

From Prabha to Everyone: 11:02 AM

Please add a few animals to do PK if the data snot available (Prabha)

From Nancy Haigwood to Everyone: 11:03 AM

Appreciate the chance to be on board.

From (b) (6) to Everyone: 11:03 AM

really happy to have you!

High-Level Meeting Summary

The Vaccines Working Group (WG) convened to hear presentations from the University of Pennsylvania, Moderna, Pfizer, and the CDC related to use of COVID-19 mRNA vaccines in pregnancy.

mRNA Vaccines and Pregnancy

Dr. Michal Elovitz, University of Pennsylvania

Risk and Benefit of Vaccines for Pregnant Women

For most individuals, the reduced risk of infection and disease after COVID-19 vaccination outweigh the risks of vaccination. Pregnancy appears to increase the risk COVID-19 morbidity and mortality: pregnant individuals are three times more likely to need ICU-level care, 2 to 3 times more likely to require a breathing tube or advanced life support, and 1.5-times more likely to die from COVID-19 than non-pregnant individuals. It is assumed that because of the increased COVID-19 risks in pregnancy, the benefits of COVID-19 vaccination also outweigh the risks during pregnancy. However, there are limitations in the data available to inform the benefit-risk assessment of COVID-19 vaccination during pregnancy.

Current Guidelines, Data, and Assumptions

The American College of Obstetrics and Gynecology and Society of Maternal-Fetal Medicine (SMFM) recommend that pregnant and breastfeeding people should be provided access to COVID-19 vaccination. SMFM and other OB-GYN professional societies have shared a fact sheets stating (as of April 6) that for COVID-19 vaccines "there is only a very small chance that they cross the placenta, so it's unlikely that they even reach the fetus, although we don't know this for sure."

Data on mRNA vaccination in pregnancy are limited. Clinical data are from the relatively small number of participants who became pregnant during clinical trials (~35 in the Moderna phase 3 trial) and the larger population (>30,000) of pregnant individuals that were vaccinated after introduction of vaccines under EUA, the earliest of which were in the second week of December (approximately 4 months ago). The CDC has reported a reassuring acute safety profile for the administration of vaccines in pregnancy, but because of the timeline since vaccine introduction, there is less information about obstetric outcomes or longer-term maternal or fetal outcomes (and see further below).

Preclinical data and developmental and reproductive toxicity (DART) studies have also been performed for the mRNA COVID-19 vaccines. These studies focus on maternal and fetal outcomes such as female reproduction, embryotoxicity, and fetal development, in animal models such as rats; DART studies did not show any adverse effects from COVID-19 vaccines. There are examples of drugs (e.g., coumadin, ACE inhibitors) that have known fetal effects when administered during pregnancy on outcomes (e.g., intraventricular hemorrhage, fetal renal injury) other than those considered in standard DART studies.

The perspectives informing the benefit-risk analysis for maternal COVID-19 vaccination include conclusions that mRNA vaccines are not teratogenic, which is supported by available evidence, and that other vaccines are safely administered in pregnancy; because there have not been prior mRNA vaccines, there is no prior experience with mRNA vaccination in pregnancy. Other commonly held perspectives include that mRNA vaccines do not reach or cross the placenta, that vaccination does not cause significant inflammation of the placenta, and that the maternal immune response to vaccination does not cause fetal harm.

Systemic Distribution and Drug Transfer

FDA regulations assume that drugs and biologics that are not detectable in maternal circulation do not pose any fetal risk. Because the placenta receives a large fraction of maternal cardiac output (second only to pulmonary vasculature), drugs and biologics present in circulation may be expected to reach the placenta; because the blood volume reaching the placenta changes across gestation, the amount of circulating drug that reaches the placenta may also vary.

For drugs that reach the placenta, some do not cross the placenta or cross with lower concentrations than observed in maternal circulation, some show the same concentrations, and some show higher concentrations. Studies have identified several factors that affect transfer across the placenta, including the molecular weight and lipid solubility of the drug.

Specific Considerations for Maternal Vaccination

One question about maternal vaccination is whether pregnant individuals develop a similar immune response to non-pregnant individuals. A recent study showed antibody titers in pregnant individuals equivalent to those in non-pregnant individuals and measured titers in cord blood that are assumed to be indicative of maternal protective responses and fetal transfer.

Another question is whether maternal vaccine responses, including side effects like fever, have consequences for fetal development. Fever is a rare side effect of other maternal vaccines, so there is limited information on the impact of fever due to vaccination on fetal development; maternal fever can be associated with neurodevelopmental consequences.

A final question is whether maternal mRNA-LNP vaccination results in lipid nanoparticles (LNP) reaching the fetus. Previous research has concluded that intramuscular (IM) mRNA-LNP administration results in systemic circulation of a fraction of the LNP that are not fully degraded at the injection site. Based on these results and previous observations that drugs distributed systemically reach the placenta, this motivated study of whether LNP can reach the placenta. Other research has shown that some other (non-lipid) nanoparticles of can cross the placenta, raising the question of whether LNP, if they reached the placenta, could also cross it. If mRNA-LNP reaches and crosses the placenta, multiple outcomes are possible: no response at all, a fetal immune response to the LNP, and fetal translation of the mRNA resulting in the production of antigen and a subsequent immune response.

Study Design

Experiments were conducted in CD-1 pregnant mice that were treated with experimental mRNA-LNP suspended in PBS (or PBS control) at 70% of gestation. Initial bioluminescence studies of high-dose (5mcg) IV administration showed evidence that experimental mRNA-LNP distributed to the uterus and placenta. The primary experiments consisted of 5 groups of 5-7 mice each; 4 groups received IM administration of mRNA-LNP and the 5th group was a control. Two of the groups received radiolabeled mRNA-LNP at 3mcg or 300ng and two of the groups received mRNA-LNP encoding a luciferase reporter at 5mcg or 50ng; the 50ng dose is roughly equivalent (to within a factor of ~2-3) to the scaled human dose of COVID-19 mRNA-LNP vaccines.

Study Results

The radiolabel experiments detected radioactivity in maternal organs, placentae, and fetuses 30-60 min following LNP injection, demonstrating systemic distribution and trafficking across the placenta; this was observed at both doses. At the 300ng dose, most maternal organs showed concentrations ~50-100% of that observed in blood; vaginal concentrations were significantly higher. The concentrations observed in the placenta and fetal membrane were similar to those in blood, and fetal concentrations were lower. The 3mcg dose showed higher levels across organs.

The luciferase experiments were intended to assess whether there was evidence of placental or fetal translation of mRNA 24 hours after administration. The assay had limited sensitivity and was only able to measure significant luciferase expression in the maternal liver. The luciferase experiments were also used to assess maternal and fetal cytokine responses, measured with a Luminex multiplex Th1 cytokine array. The assays were performed on maternal serum, amniotic fluid, placental, and fetal liver samples; cytokines in the amniotic fluid are attributed to the fetal membrane or fetus based on the understanding that maternal cytokines do not cross the placenta.

At the 5mcg dose, maternal serum and amniotic fluid showed significantly elevated cytokine levels; the significantly elevated cytokines were different between maternal serum and amniotic fluid, with the amniotic fluid showing both Th1 and Th2 cytokines at elevated levels. At the 5mcg dose the placenta showed elevated levels of 4 cytokines which were also elevated in the maternal serum, and the fetal liver showed 1 elevated cytokine which was also elevated in the amniotic fluid. At the 50ng dose there were only 3 statistically significant changes in cytokine levels: one in amniotic fluid and two in fetal liver; one of those 3 changes, in fetal liver, was consistent with a significant change at the higher dose. Both placenta and fetal liver express APOE, thus immune response to LNP is plausible.

Conclusions and Next Steps

These studies indicate that mRNA-LNP delivered via IM injection to pregnant mice can reach and cross the placenta. These results are consistent with existing literature showing that mRNA-LNP can reach systemic circulation and that systemic circulation can deliver drugs and biologics to the placenta. These studies also indicate that mRNA-LNP can cross the placenta and be taken up in the fetus, which is consistent with similar findings for some non-lipid nanoparticles of similar size and charge. These findings do not support a perspective that mRNA-LNP cannot achieve systemic circulation and reach the placenta and fetus.

When sufficient experimental mRNA-LNP reached the fetal-placental unit, significantly elevated levels of cytokines indicative of an inflammatory immune response were observed. The consequences of an immune response in the fetal-placental unit are unknown; other research studying maternal inflammation has found associations with long-term neurobehavioral outcomes that are not apparent from gross histopathology or post-natal evaluation. It is not known whether fetal translation of mRNA could occur or what the results of potential fetal production of spike protein (e.g., protection, tolerance) would be.

This research team believes that these results motivate informing pregnant individuals that mRNA-LNP can reach and cross the placenta. Suggested research includes mouse, NHP, and clinical studies of mRNA-LNP in the maternal-fetal context. This research team has funding to look at cord blood from individuals vaccinated during pregnancy to study innate and humoral immune responses, and will perform additional mouse studies looking at fetal translation of the spike protein, gestational-age-dependent effects, and neurobehavioral outcomes.

Discussion

(b) (4) [redacted] *Outcomes*

Dr. (b) (4), (b) (6) [redacted] (b) (4) [redacted] Dr. (b) (4), (b) (6) [redacted] noted that this study (b) (4) [redacted]

Comparison to Other (b) (4) [redacted]:

Dr. (b) (4), (b) (6) [redacted] asked (b) (4) [redacted]. Dr. (b) (4), (b) (6) [redacted] stated (b) (4) [redacted]

Dr. (b) (4), (b) (6) [redacted] noted (b) (4) [redacted] Dr. (b) (4), (b) (6) [redacted] shared (b) (4) [redacted]

Dr. (b) (4), (b) (6) [redacted] suggested (b) (4) [redacted] study. Dr. (b) (4), (b) (6) (b) (4).

Dr. (b) (4), (b) (6) (b) (4). Dr. (b) (4), (b) (6) (b) (4). Dr. (b) (4), (b) (6) noted (b) (4)

Animal Model Limitations

There was discussion of the limitation of the mouse model and questions about translation to clinical outcomes, including the general observation that some mouse studies do not predict human results, and specific questions about whether the mouse placenta and placental trafficking were good models and whether there are validated animal models for neurodevelopmental outcomes. Dr. Elovitz acknowledged that there are limitations to mouse models but observed that mouse studies are routinely used for drug and vaccine research and rodent studies are used for regulatory DART studies.

In the meeting (b) (4). Dr. (b) (4), (b) (6) suggested that follow up with Dr. (b) (4), (b) (6) (b) (4) Dr. (b) (4), (b) (6) could join].

Dr. (b) (4), (b) (6) (b) (4) Dr. (b) (4), (b) (6) noted (b) (4)

Differences in (b) (4).

Dr. (b) (4), (b) (6) noted (b) (4) Dr. (b) (4), (b) (6) noted (b) (4)

mRNA-LNP Distribution and Degradation

Dr. Ann Arvin asked what is known about the distribution of the mRNA vaccines in NHP models. Dr. Elovitz noted that mouse data show mRNA-LNP distributed to lymph nodes, and reiterated that literature on non-lipid nanoparticles that are designed for trans-placental delivery show that some nanoparticles can cross the placenta. Dr. Jansen noted that work published by Dr. Weissman indicates that different LNPs distributed differently and warned about making general inferences about LNPs from observations for a specific LNP.

Dr. (b) (4), (b) (6) [redacted] asked (b) (4) [redacted] Dr. (b) (4), (b) (6) [redacted] that Dr. (b) (4), (b) (6) [redacted] (b) (4) [redacted] Dr. Miller stated (b) (4) [redacted]

Considerations for Findings

(b) (4) [redacted] Dr. (b) (4), (b) (6) [redacted] discussed (b) (4) [redacted]

Use of Real-World Data to Evaluate Safety and Effectiveness of Moderna COVID-19 Vaccine in Pregnancy

Dr. Jacqueline Miller, Moderna

Challenges to Evaluating Vaccination in Pregnancy

When a vaccine is already in widespread use and recommended for use in pregnancy, it is challenging to conduct ethical clinical trials in pregnant populations. Flu and Tdap vaccines were recommended for use during pregnancy, but it was desirable to conduct trials to inform public health decisions. The lesson from working on those vaccines is that, when the vaccine is already recommended, a well-controlled clinical trial for pregnant individuals can take years to design and implement (e.g., several years from starting the design to final results for Tdap).

COVID-19 vaccines are in a similar circumstance. The current Moderna vaccine fact sheet states that there is not information on the use of the vaccine during pregnancy. However, based on current recommendations, many pregnant individuals have received the vaccine. Moderna is generating pregnancy-related data to complement CDC's data (described below) in its ongoing vaccine clinical trial, a long-term effectiveness trial, a prospective observational pregnancy outcomes study, and a secondary database study.

mRNA-1273-P301 Clinical Trial

The ongoing mRNA-1273-P301 clinical trial has 50 pregnancies reported within its participant population. Of these pregnancies, 10 have ended in spontaneous abortion or elective termination, and 1 was lost to follow-up; the remaining 39 are ongoing. The Moderna DSMB continues to review data collected on these pregnancies and thus far has not identified any safety concerns.

Long-Term Effectiveness Study

The long-term effectiveness study is a prospective observational database study to evaluate real-world Moderna vaccine effectiveness and durability of protection among diverse populations in a large integrated healthcare system. Moderna has collaborated with Kaiser Permanente to evaluate medical records of adults in Southern California who have had Kaiser Permanente health insurance for at least 1 year; the goal is to obtain a sample size of 500K to 1M individuals by the end of 2021. The primary objectives of this study are to evaluate the effectiveness of two doses of Moderna vaccine in preventing SARS-CoV-2 infection, COVID-19 disease, and severe outcomes. The secondary outcome is to evaluate the effectiveness and durability of the Moderna vaccine in preventing COVID-19 in relation to five categories: (1) age and sex, (2) racial/ethnic groups, (3) pregnancy, (4) patients with chronic diseases, and (5) immunocompromised patients. This study will also link PCR-confirmed infections with sequencing to evaluate the effectiveness of vaccination against viral variants.

Observational Pregnancy Outcomes Study

The prospective observational pregnancy outcomes registry study will enroll pregnant individuals who have received the Moderna vaccine in the U.S., Canada, Germany, Italy, and Finland. Study endpoints include pregnancy outcomes and complications as well as infant outcomes through 1 year. Study data will be compared to external data to identify increased risks. This study is currently awaiting PRAC endorsement and is expected to be initiated in the coming months.

Secondary Database Study

The secondary database study with the Vaccine Monitoring Collaboration for Europe (VAC4EU) leverages routinely collected healthcare data in Denmark, Norway, UK, Italy, and Spain to evaluate pregnancy outcomes and complications as well as infant outcomes. Moderna and VAC4EU are currently developing the study protocol.

Discussion

Dr. Elovitz asked whether infants in the various Moderna studies will be evaluated during the first year of life. Dr. Miller noted that infants will be followed in the registry study and that work is in progress to determine how to link infant data in the database studies.

Dr. Michael Santos asked about Moderna's DART results. Dr. Miller responded that Moderna's DART results did not identify any changes in fertility, pregnancy, or infant outcomes in rats; rat studies indicated that IgG was able to cross the placenta.

Pfizer's BNT162b2 Nonclinical Safety Package and DART Study

Dr. Cindy Rohde, Pfizer

Overview

The DART study was performed in a similar repeat-dose rat model study design as was used for the nonclinical safety package. This model included IM vaccine administration at 1-week intervals. The safety studies included microscopic tissue assessment of reproductive organs, and did not identify any vaccine-related findings.

DART Study

The DART study was conducted to assess fertility, pregnancy, and development outcomes in rats receiving four IM administrations of the vaccine at the human dose (30 mcg). Two of these doses were administered prior to mating the female rats with untreated breeder male rats and two doses were administered after mating and during gestation. Half of the females receiving vaccine doses underwent a C-section on gestation day 21 and both the female and fetuses were evaluated for visceral and skeletal abnormalities, as well as immune responses. The remaining females naturally gave birth and both females and pups were followed through postnatal day 21 (the end of weaning); the pups were assessed for developmental outcomes, including pupillary response, startle response, and eye-opening time. All females, fetuses, and pups displayed a vaccine antigen-specific neutralizing antibody response. No effects were observed on fetal and pup growth, development, or survival or on female mating performance, fertility, or ovarian/uterine parameters. Some vaccine-related maternal observations were observed, particularly local injection site reactions and weight fluctuations.

Discussion

Dr. Elovitz asked what ovarian/uterine parameters were evaluated and what immune responses were observed. Dr. Chris Bowman noted that the corpora lutea were counted in relation to the number of implantation sites were identified in the uterus; this process counts both the number of resorptions and live fetuses. The immune responses measured were neutralizing antibody responses; other types of responses, such as cytokines, were not measured. Dr. Burkhardt suggested that additional exploratory data with additional controls, including looking at other maternal vaccines, would be of interest.

Dr. Jansen observed that the DART study was in a standard model that is generally accepted as being predictive based on the outcomes that are evaluated, and asked whether there are validated preclinical models for the outcomes discussed by Dr. Elovitz (e.g., neurodevelopmental outcomes that are not immediately evident) that could be used to inform these questions prior to the availability of clinical data. Dr. Elovitz stated that there are preclinical models of neurodevelopmental outcomes, but that there is a challenge with the time required to complete them. Dr. Burkhardt said that there are models similar to the DART study that follow pup developmental outcomes out to 90 days, that have been validated in the context of drug development.

COVID-19 Vaccine Safety in Pregnancy

Dr. Tom Shimabukuro, CDC

Overview

The CDC's Immunization Safety Office supports three core programs (i.e., Vaccine Safety Datalink [VSD], Clinical Immunization Safety Assessment [CISA], and Vaccine Adverse Event Reporting System [VAERS]), as well as two new programs initiated during the COVID-19 pandemic (i.e., v-safe and v-safe Pregnancy Registry).

Core Surveillance Programs

VSD is the CDC's active surveillance and research system that includes nine participating integrated healthcare organizations, with data on more than 12 million individuals per year. During the COVID-19 pandemic, VSD collects data on COVID-19 vaccine coverage in pregnancy, risk of miscarriage and stillbirth following COVID-19 vaccination, and safety in pregnancy (e.g., adverse events in pregnancy and infant follow-up). CISA includes seven participating medical research centers with vaccine safety experts and collects information at each center related to clinical consult services and clinical research for COVID-19 (particularly adverse events, local and systemic reactogenicity, and infant health outcomes during the first 3 months of life). CISA will include a prospective observational cohort study that will collect adverse pregnancy and birth outcomes and infant health outcomes to 3 months of age.

VAERS is the nation's early warning system for vaccine safety, for which individuals, providers, etc., share information related to vaccine safety. As of February 16, 2021, 154 pregnancy reports had been collected in VAERS; the number is substantially higher now. Approximately half of the reports were for vaccination in the first trimester. Seventy-three percent of the adverse events reported during pregnancy were not pregnancy-specific (including headaches and fatigue). The pregnancy-specific outcomes were consistent with expectations based on typical pregnancy outcomes (e.g., spontaneous abortion); VAERS does not have denominator data, but no specific safety signals have been noted among these reports.

COVID-19 Programs

v-safe is the CDC's smartphone-based active safety monitoring system for individuals who receive a COVID-19 vaccine. After receiving a vaccination, individuals are prompted to complete daily surveys for 1 week, then weekly surveys for 6 weeks, and then quarterly surveys through 12 months. To date, approximately 7.5M individuals have registered with v-safe and of these registrants approximately 78K participants have reported being pregnant. Preliminary data indicates similar rates of local reactions (pain, swelling, redness, and itching) for pregnant and nonpregnant women between the ages of 16 and 54 who have received the Pfizer-BioNTech dose 1 and 2 and Moderna dose 1 vaccines. These data also indicate that pregnant and nonpregnant women display similar rates of systemic reactions (fatigue, headache, myalgia, chills, nausea, and fever) after receiving either dose of the Pfizer-BioNTech or Moderna vaccine.

v-safe participants who are pregnant are contacted by the pregnancy registry team to assess eligibility and to obtain consent for follow-up (up to 3 months postnatal) and enrollment into the v-safe Pregnancy Registry. Approximately 4K pregnant individuals have enrolled in the v-safe Pregnancy Registry, of which 275 had completed their pregnancies by Feb 19. CDC has compared pregnancy outcomes and complications data, as well as neonatal outcomes data, within the v-safe Pregnancy Registry to overall background rates and found that they were comparable, with the caveat that completed pregnancies are typically for individuals vaccinated later in pregnancy.

Conclusions and Next Steps

Together, data from each of these CDC programs enable the collection of safety data related to vaccines and pregnancy, which were not studied in preauthorization clinical trials. Thus far no safety signals associated with reactogenicity, pregnancy, or birth outcomes have been identified. Enrollment into v-safe and the v-safe Pregnancy Registry has surpassed expectations and thus substantial additional data are expected.

Appendix A: Participants List

WORKING GROUP MEMBERS

Kathrin Jansen, PhD, *Senior Vice President, Head of Vaccine Research and Development, Pfizer*
Douglas Lowy, MD, *Principal Deputy Director, NCI, NIH*
Paula Annunziato, MD, *Vice President, Vaccine Clinical Development, Merck*
Ann Arvin, MD, *Professor of Pediatrics and Microbiology & Immunology, Stanford University*
Susan Buchbinder, MD, *Director of Bridge HIV, San Francisco Department of Public Health, and Professor, UCSF*
Larry Corey, MD, *Professor and Principal Investigator, University of Washington and HIV Vaccine Trials Network, and Past President and Director, Fred Hutchinson Cancer Research Center*
Peter Hotez, MD, PhD, *Dean for the National School of Tropical Medicine, Baylor College of Medicine, and Director, Texas Children's Center for Vaccine Development*
Antonio Lanzavecchia, MD, *Director, Immune Regulation, Institute for Research in Biomedicine*
Peter Marks, MD, PhD, *Director, Center for Biologics Evaluation and Research, FDA*
Paul Offit, MD, *Professor, University of Pennsylvania, and Director, Vaccine Education Center, Children's Hospital of Philadelphia*
Michael Santos, PhD, *Associate Vice President, Science, Foundation for the NIH (FNIH)*
Brett Tolman, MA, *Strategy Manager, Deloitte*
Tonya Villafana, PhD, MPH, *Vice President, Global Franchise Head, Infection, AstraZeneca*

INVITED PARTICIPANTS

Judith Absalon, MD, MPH, *Senior Medical Director, Vaccine Clinical Research, Pfizer*
Melissa Arvay, PhD, MPH, *Epidemiologist, CDC*
Richard Beigi, MD, MSc, *Professor, Reproductive Sciences, Department of Obstetrics, Department of Gynecology and Reproductive Sciences, University of Pittsburgh*
Diana Bianchi, MD, Director, *NICHD, NIH*
Adam Bloomfield, MD, *Senior Director, Global Medical Affairs, Moderna*
Karin Bok, PhD, MS, *Senior Advisor, Vaccine Research Center, NIAID, NIH*
Chris Bowman, PhD, *Research Fellow, Pfizer*
John Burkhardt, PhD, DVM, *Head of Global Drug Safety Research and Development, Head of Comparative Medicine, Pfizer*
Myron Cohen, MD, *Director for Global Health & Infectious Diseases, University of North Carolina (UNC) School of Medicine*
Michelle Culp, BSN, MPH, *Senior Advisor, Office of Science Policy, NIH*
Gary Dubin, MD, *Senior Vice President and Head of Global Medical Office, Takeda*
Michal Elovitz, MD, *Director, Maternal and Child Health Research Center, Department of Obstetrics and Gynecology, University of Pennsylvania*
Sascha Ellington, MSPH, CPH, *Epidemiologist, CDC*
Emily Erbelding, MD, MPH, *Director, Division of Microbiology and Infectious Diseases, NIAID, NIH*

Ellen Gadbois, PhD, *Program Lead, Biosafety, Biosecurity, and Emerging Biotechnology Policy Division, Office of Science Policy, NIH*

Gregory Glen, MD, *President, Research and Development, Novavax*

Antonio Gonzalez-Lopez, MD, *Global Clinical Head, COVID-19 Vaccine US Program, AstraZeneca*

Holli Hamilton, MD, MPH, *Senior Medical Officer, BARDA*

Brenna Hughes, MD, *Associate Professor of Obstetrics and Gynecology, Duke University of Medicine*

Randall Hyer, MD, PhD, *Senior Vice President, Global Medical Affairs, Moderna, Inc.*

Denise Jamieson, MD, MPH, *Chair and Professor, Department of Gynecology and Obstetrics, Emory University School of Medicine*

Joanne Lumsden, PhD, *Senior Scientific Program Manager, Drug Development Partnership Programs, NCATS, NIH*

Mary Marovich, MD, *Director, Vaccine Research Program, NIAID, NIH*

Susan Mather, MD, *Senior Director, Safety Surveillance and Risk Management, Pfizer*

Dana Meaney-Delman, MD, MPH, *Medical Officer, National Center on Birth Defects and Developmental Disabilities, CDC*

Jacqueline Miller, MD, *Senior Vice President, Therapeutic Area Head, Infectious Disease, Moderna, Inc.*

Kathy Neuzil, MD, MPH, FIDSA, *Director, Center for Vaccine Development and Global Health, University of Maryland School of Medicine*

Titilope Oduyebo, MD, MPH, *Adjunct Assistant Professor, Obstetrics and Gynecology, Emory School of Medicine*

Sara Oliver, MD, MPSH, *Epidemic Intelligence Service Officer, Division of Viral Diseases, CDC*

Ashley Parker-Gordon, PhD, *Health Science Policy Analyst, NIH*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH*

Laura Riley, MD, *Obstetrician and Gynecologist-in-Chief at New York Presbyterian/Weill Cornell Medical Center*

Merlin Robb, MD, *Chief Medical Advisor, Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc.*

Cindy Rohde, PhD, *Associate Research Fellow, Pfizer*

Tom Shimabukuro, MD, MPH, MBA, *Deputy Director, Immunization Safety Office, CDC*

Vivek Shinde, MD, MPH, *Vice President, Vaccine Clinical Development, Novavax*

Mark Sotir, PhD, *Epidemiologist, CDC*

Geeta Swamy, MD, *Associate Vice President for Research, Duke University*

Kimberly Taylor, PhD, *Chief, Biodefense Vaccines and Other Biologics Development Section, NIAID, NIH*

Natalie Thornburg, PhD, *Lead Microbiologist, Respiratory Viruses Branch, CDC*

Chris Zahn, MD, *Vice President, Practice Activities at American College of Obstetricians and Gynecologists*

Roland Zahn, PhD, *Senior Scientific Director, Preclinical Immunology, Viral Vaccines, Janssen*

FNIH STAFF

Stacey Adam, PhD, *Director, Cancer, FNIH*
Joseph Menetski, PhD, *Associate VP of Research Partnerships, FNIH*
David Wholley, MPhil, *Senior VP of Research Partnerships, FNIH*

Bethany Stokes, MS*, Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

From Dr Brenna Hughes, M.D. to Everyone: 02:29 PM

Thanks Michal- did you look at any pregnancy outcomes (pup loss etc) in your model.

From pauloffit to Everyone: 02:29 PM

Are you going to wait to show whether you have any evidence of harm to the pup before you publish these data, which might otherwise be misinterpreted?

From Richard Beigi to Everyone: 02:32 PM

The association with neurobehavioral outcomes from intrauterine inflammation has been among babies with chorio. Can you translate levels of cytokines found here from bacterial infections to the seemingly marginal findings noted in these mice, apparently from vaccine?

Chorio is noted to have a massive inflammatory reaction - it is not clear to me that this approximates that level of correlation

From John B to Everyone: 02:32 PM

Based upon your historical control range of data for cytokines, the slight variations observed are of small magnitude. Is it difficult to interpret these small magnitudes?

From jansenk2 to Everyone: 02:32 PM

have the experiments be repeated with dose evels that are the ones used in humans?

From John B to Everyone: 02:33 PM

Given the difference in anatomy of rodent vs. human placentation, is it overly speculative to assume exposure across placenta in human, based upon rodent data?

From Dr Brenna Hughes, M.D. to Everyone: 02:33 PM

Cytokine data are a response to a pathologic process. There is evidence that there is some increase in cytokines after flu vaccine and we know that it is associated with improved outcomes.

From annarvin to Everyone: 02:34 PM

Has this model been used to evaluate other vaccines given in pregnancy?

From jansenk2 to Everyone: 02:34 PM

what is the correlation between a marginal cytokine increase in the mouse and assuming such potential marginal increase in a pregnant women to outcome in baby?

From Emily Erbelding to Everyone: 02:37 PM

Can someone comment on whether the mouse placenta is good one for extrapolation to humans for vaccine?

From Jacqueline Miller- Moderna to Everyone: 02:40 PM

I noted that there were some inconsistent responses between the two different dose levels. What is the variability of these assays on which conclusions are drawn?

From Dr Brenna Hughes, M.D. to Everyone: 02:42 PM

@emilyerbelding Mouse models are generally considered a good starting point for placental drug transfer studies.

From jansenk2 to Everyone: 02:42 PM

let's discuss DART studies and what they are validated and designed to do; there are validated models to assess potential neuro outcomes in babies; can we ask what they are and how these models differ from what was just presented?

From Michal Elovitz to Everyone: 02:53 PM

any effort to follow infants up to a year?

From Michal Elovitz to Everyone: 03:01 PM

what immune responses were assessed?

From Karin Bok to Everyone: 03:08 PM

Are you using the same approach for your maternal RSV vaccine

From John B to Everyone: 03:10 PM

The approach described for this vaccine is analogous to that used for maternal RSV vaccine and other maternal vaccines.

From Geeta Swamy, M.D. to Everyone: 03:13 PM

we have good data on maternal cytokine response following influenza vaccine and the cytokine response is slightly elevated and returns to baseline within ~ 7 days

same with tdap

From Dr Brenna Hughes, M.D. to Everyone: 03:15 PM

Michal one more question- possibly naïve. How does what you used the lnp relate to the mRNA vaccines that are being used clinically.

From lowyd to Everyone: 03:15 PM

Although the HPV vaccine is a different platform, HPV is reported to be transmitted from mother to child at readily detectable rates. It was postulated such transmission could induce immune tolerance. However, there is no evidence of immune tolerance in HPV vaccines

From Jacqueline Miller- Moderna to Everyone: 03:15 PM

It would seem like the fact that placental transfer of influenza and pertussis antigens across the placenta would be a good reason to test those vaccines in Dr. Elovitz's model- one would expect a lack of increase of Th-1 cytokines in these cases

From Michal Elovitz to Everyone: 03:15 PM

same as Pfizer. slightly different from moderna

From Dr Brenna Hughes, M.D. to Everyone: 03:15 PM

So it was the Pfizer vaccine?

From Michal Elovitz to Everyone: 03:17 PM

DPT and Flu antigens from vaccine do not transfer to the fetus

From jansenk2 to Everyone: 03:17 PM

no it was not; Michal as asked before please provide the exact composition of the vaccine that was used in your model together with quality control data that the material did not contain endotoxin or other compounds that may affect outcome

From Michal Elovitz to Everyone: 03:21 PM

the LNP is from Drew Weissman's laboratory. I can have him share the exact formulation.

From Emily Erbelding to Everyone: 03:25 PM

was the LNP given a GMP lot?

From John B to Everyone: 03:25 PM

Certificate of Analysis for the material dosed would be ideal to have.

From jansenk2 to Everyone: 03:27 PM

not likely as we never provided GMP material for this work; it is my understanding it was some research material and to this date we have not received the exact composition despite having asked for it

From Michael Santos to Everyone: 03:27 PM

My apologies that we weren't able to schedule this meeting at a time that Drew could join - we tried but with so many schedules we unfortunately couldn't accommodate every schedule.

From Michal Elovitz to Everyone: 03:28 PM

I would suggest that it would be most appropriate to have a follow up conversation with Drew.

From Karin Bok to Everyone: 03:28 PM

The pregnancy RSV vaccine currently being tested in Phase 3 trials under FDA review is similar in design to the coronavirus vaccine and potential to cross placenta. Did FDA require any additional studies to move forward with a pregnancy trial? Did they feel it was needed to require other studies even though it is a new class of vaccines for pregnancy as well?

From jansenk2 to Everyone: 03:30 PM

there are a number of RSV vaccines that are tested in maternal studies; which one are you referring to?

From pauloffit to Everyone: 03:31 PM

CDC should follow up these children for at least one year

From Dr Brenna Hughes, M.D. to Everyone: 03:37 PM

Even live virus vaccines, while not given in pregnancy, haven't been associated with adverse outcomes when received inadvertently despite theoretical concerns.

High-Level Meeting Summary

The Leadership Team and Executive Committee ("Leadership Team") guiding the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) Partnership convened to review the status of current ACTIV efforts, presented by Co-Chairs of the Preclinical, Therapeutics Clinical (TX-Clinical), and Vaccines Working Groups (WGs).

Preclinical WG

John Young, PhD, Roche; Christine Colvis, PhD, NCATS

Preclinical WG Co-Chairs provided updates on two of the WG's urgent and ongoing activities: (1) preclinical agent prioritization and matchmaking efforts and (2) national tracking, testing, and reporting of emergent SARS-CoV-2 variants and their impact on the efficacy of therapeutics and vaccines.

Agent Prioritization and Matchmaking

The Preclinical WG has now evaluated a total of 137 agents (10 since the December Leadership Team meeting); the rate of new submissions has begun to slow. Of all the agents evaluated, 25 have been identified as eligible for matchmaking. Detailed information on the class and status of those agents selected is available in the slide deck appendix prepared for this meeting.

Tracking of Emergent SARS-CoV-2 Variants

Following directives from the ACTIV Leadership Team, the WG has been developing a strategy for evaluating emerging SARS-CoV-2 variants and for rapidly sharing data related to those variants, to predict their potential to resist therapeutics or escape vaccines, as well as to mitigate these dangers in real time. The WG has outlined several central aims of its strategy for these efforts, which are summarized below:

- Coordinating data, resources, and recommendations for rapid and comparable results
- Prioritizing variants based on threat level assessment
- Validating therapeutic impact of priority variants in biochemical and cellular infection assays as well as in animal models
- Ensuring rapid public access to results to inform real-time clinical decision making and to ensure optimal use by the R&D community in fighting the pandemic

Since the December Leadership Team meeting, the Preclinical WG has begun assembling five expert subteams that will provide guidance on key variant tracking needs and has met with industry partners to discuss assay harmonization and data sharing/coordination. The WG is planning to leverage ongoing National Center for Biotechnology Information (NCBI) efforts to provide viral sequence data and analytics to the public in real time.

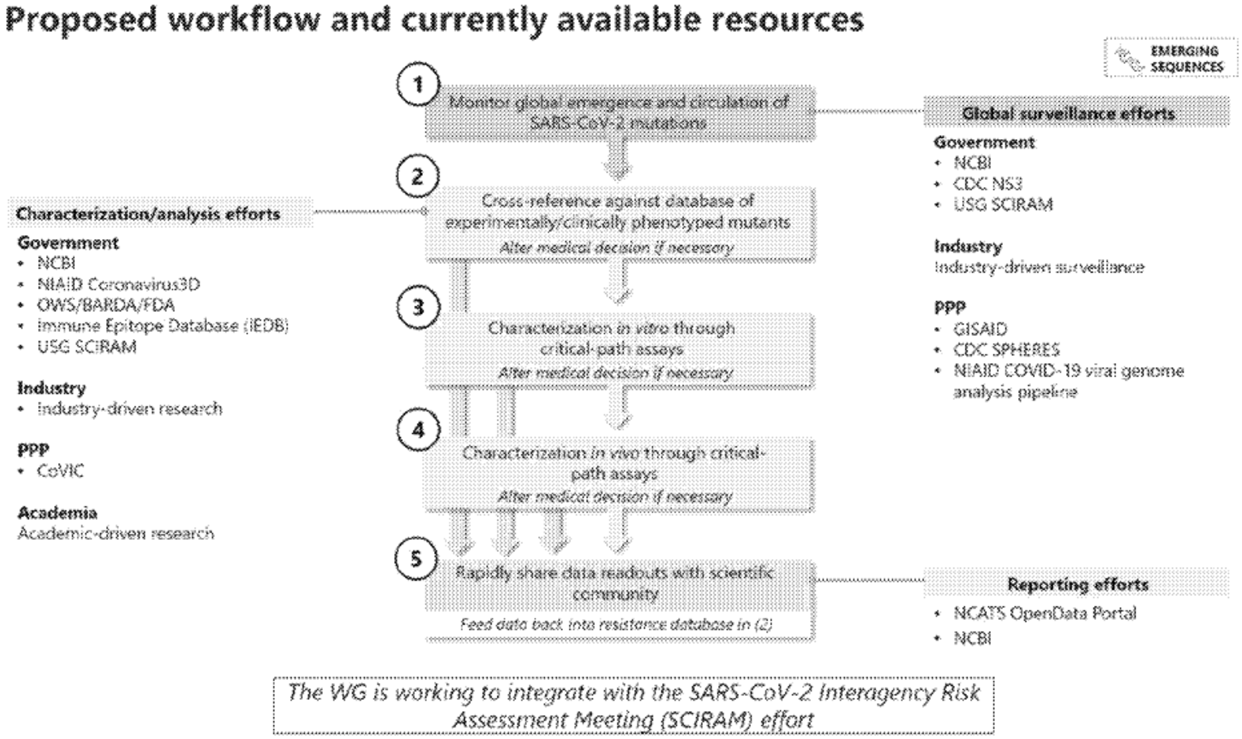
The five key needs that the expert subteams are focusing on include the following:

1. Establish criteria for prioritizing emerging variants

2. Identify critical assays to be conducted sequentially or in parallel
3. Provide guidance for producing high-quality reference materials such as growth of virus isolates and standard plasma samples (convalescent and post-vaccination)
4. Outline a rapid and high-quality deep sequencing pipeline for variant confirmation
5. Share phenotypic and sequence data from industry partners

The subteams each include experts from industry, NIH, and other government agencies, who in addition to providing expert guidance for ACTIV's emerging SARS-CoV-2 variant tracking, will be crucial for avoiding duplication of efforts across these stakeholder groups.

The graphic below depicts the Preclinical WG's proposed workflow for its variant tracking efforts:


Proposed workflow and currently available resources
EMERGING SEQUENCES
1
Monitor global emergence and circulation of SARS-CoV-2 mutations
Global surveillance efforts
Government
NCBI
CDC NS3
USG SCIRAM
Industry
Industry-driven surveillance
PPP
GISAID
CDC SPHERES
NIAID COVID-19 viral genome analysis pipeline
2
Cross-reference against database of experimentally/clinically phenotyped mutants
Alter medical decision if necessary
Characterization/analysis efforts
Government
NCBI
NIAID Coronavirus3D
OWS/BARDA/FDA
Immune Epitope Database (IEDB)
USG SCIRAM
Industry
Industry-driven research
PPP
CoVIC
Academia
Academic-driven research
3
Characterization in vitro through critical-path assays
Alter medical decision if necessary
4
Characterization in vivo through critical-path assays
Alter medical decision if necessary
5
Rapidly share data readouts with scientific community
Feed data back into resistance database in (2)
Reporting efforts
NCATS OpenData Portal
NCBI
The WG is working to integrate with the SARS-CoV-2 Interagency Risk Assessment Meeting (SCIRAM) effort

The Global Initiative on Sharing Avian Influenza Data (GISAID), one public-private partnership listed under "Global surveillance efforts" above, is an international effort whose infrastructure for sharing information on global influenza variants is being adapted for SARS-CoV-2. Although GISAID supports rich variant data, data availability is limited. CDC's SARS-CoV-2 Sequencing for Public Health Emergency Response, Epidemiology, and Surveillance (SPHERES) is a U.S.-based program with Canadian and U.K. components that is prioritizing public data sharing, including rapid release of viral sequence data for emerging SARS-CoV-2 strains from clinical and public health laboratories. Specifically, SPHERES deposits data into GISAID's and NCBI's databases in near real time.

The envisioned timeline for the WG's emerging variant monitoring efforts is shown below:

(b) (4) [redacted]

Because many of the activities listed above will require funding that is not yet available, months specified at the top of the timeline indicate number of months *after* funding becomes available. Some activities that can be completed without funding are now being pursued.

Discussion

Dr. Francis Collins emphasized the critical importance of the Preclinical WG's efforts to track, evaluate, and share information on emerging SARS-CoV-2 variants, and to coordinate ongoing efforts to avoid duplication. He added that Dr. (b) (6) [redacted] (b) (4) [redacted]

Participants pointed to several elements of the variant tracking landscape that the Preclinical WG should be aware of as they pursue these efforts. Dr. Collins noted that CDC's efforts to sequence SARS-CoV-2 strains from patient samples across the United States have increased dramatically; these efforts include new CDC contracts with LabCorp and Illumina, which are likely to further expand sample collection and sequencing. Dr. Gary Disbrow suggested that the Preclinical WG also liaise with the Department of Defense Global Emerging Infections Surveillance (GEIS) group. He will suggest a specific GEIS contact to Dr. Colvis offline.

Dr. Young emphasized that many companies possess crucial information on emerging variants (e.g., the B1.1.7 and 501.V2 variants), and that a key priority is to encourage prompt release of this information with researchers outside of those companies.

Therapeutics-Clinical WG

Sarah Read, MD, NIAID; Eric Hughes, MD, PhD Novartis

Master Protocol Subgroup

Dr. Sarah Read summarized the status of ACTIV's master protocols:

- **ACTIV-1:** phase III; immune modulators; inpatients
    - **Status:** 28 sites (plus 3 satellite sites) and 198 participants as of January 14; currently activating additional sites; submitted Amendment 1 to IRB on December 3 and to FDA on December 4 to streamline enrollment and allow co-enrollment with ACTIV-4a; conducted DSMB review on January 7 resulting in "safe to proceed"; continuing to evaluate and select participating sites
    - **Sponsor:** Duke Clinical Research Institute (DCRI) + NCATS Trial Innovation Network (TIN) + TRI
    - **First agents**: abatacept, infliximab, cenicriviroc
- **ACTIV-2:** phase II/III; neutralizing antibodies (nAbs) and oral antivirals; outpatients
    - **Status:**
        - (b)(4) 94 sites and (b)(4) as of January 13
        - (b)(4) 11 sites open and (b)(4) as of January 13
        - FPI for (b)(4) (V2) on January 5; (b)(4) open-label study will close after January 15
        - Version 3.0 submitted to FDA on December 22
    - **Sponsor:** NIAID AIDS Clinical Trials Group (ACTG) + CRO
    - **Future agents:** nAbs from AstraZeneca and RU-BMS; polyclonal antibody from SAB; inhaled IFN-beta from Synairgen; and camostat mesylate from Sagent
- **ACTIV-3:** phase II/III (will include phase I testing option for agents that need it); neutralizing monoclonal nAbs; inpatients
    - **Status:** 30 sites and (b)(4) for (b)(4) as of January 14; Version 3 submitted to FDA and central IRB on December 15; FDA issued "safe to proceed" for ACTIV-3 Version 2 with feedback about how to monitor for allergic reactions (safety review with DSMB to occur on January 25); ACTIV-3b/TESICO protocol studying Aviptadil in severely ill patients, reviewed by DSMB on January 4 but not yet submitted to FDA
    - **Sponsor:** NIAID INSIGHT + NHLBI PETAL + NHLBI CTSN + VA + CRO
    - **Future agents**: nAbs from (b)(4), and DARPin from (b)(4)
- **ACTIV-4:** phase III; anticoagulants; inpatients (cohorts: pre-hospitalized, hospitalized, post-hospitalized)
    - **Status:** 54 sites and (b)(4) enrolled as of January 13 in hospitalized cohort (DSMB met on December 16 and recommended enrollment in moderately ill patients only, pausing enrollment of severely ill patients because they could not rule out the possibility of harm); 11 sites and 85 participants in pre-hospitalized cohort as of January 13; post-hospitalized cohort received first drug shipment on January 5
    - **Sponsor:** NHLBI-NINDS CONNECTS Network

  - **First agents:** hospitalized: low molecular weight heparin and unfractionated heparin; pre-hospitalized: low dose aspirin, high dose aspirin, and apixaban
- **ACTIV-5:** phase II; proof of concept study to identify promising treatments; inpatients
  - **Status:** 9 sites and (b) (4) [redacted] as of January 13; prioritizing additional investigational agents
  - **Sponsor**: NIAID + IDCRC + Leidos
  - **First agents:** risankizumab and lenzilumab

Dr. Read presented the table below capturing the status of various ACTIV trial team activities:

Initiative & Description	Status	Progress / Next Steps
(b) (4) [redacted]	*In-Progress*	• (b) (4) [redacted] partners completed the initial site search for ACTIV-1 and are conducting additional refinements to their search • (b) [redacted] partners completed the initial site search for ACTIV-2 and have identified ~1,260 potential sites for further assessment • **Next Steps:** *ACTIV-1 and -2 trial teams are following up with interested sites; ACTIV-3, -4, and -5 trial teams will be offered the collaboration next*
Site Staffing Augmentation Partner with (b) (4) [redacted] to contract a team of Site Specialists who can help with site activation and recruitment for all ACTIV trials	*In-Progress*	• ACTIV released a Request for Information (RFI) to ACRO members and received responses from [redacted] (b) [redacted] • **Next Steps:** *ACTIV is in process of facilitating vendor evaluation and contracting with ACTIV 1 through 4 trial teams*
Society for Clinical Research Sites (SCRS) Share information on ACTIV trials with 9500+ SCRS member sites to recruit additional clinical sites for ACTIV studies	*In-Progress*	• ACTIV has developed and shared trial descriptions and contact information for posting to the SCRS Trial Opportunity Platform and conducted a webinar for SCRS sites • **Next Steps**: *Platform had ~600 views in December. SCRS is putting interested sites in contact directly with ACTIV trial teams for vetting and activation*
Site Identification & Outreach Engage with networks and integrated health systems (e.g., NCI NCORP, NIGMS / IDeA network, PCORnet, etc.) to identify additional clinical sites for ACTIV studies	*In-Progress*	• ACTIV held webinars on Nov 4 and Dec 22 to provide an overview of the ACTIV trials • As of January 8, interest expressed from at least 31 sites; 9 of those sites are already supporting ACTIV trials (5 are supporting more than one trial) • **Next Steps:** *Trial teams to continue connecting with and vetting interested sites*
CVS Health Partnership Partner with CVS Health to provide patient referrals and home health resources	*In-Progress*	• ACTIV-2: Contract has been signed; CVS is actively referring patients • ACTIV-4b: Contract is being finalized (targeting late January for activation) • **Next Steps:** *Finalize ACTIV-4b agreement and expand ACTIV-2 agreement to provide more patient referrals*
HHS Portal and Call Center "Combat COVID" Portal provides resources to prospective participants interested in COVID-19 clinical trials, who can be centrally triaged to eligible trial(s) from a call center	*Complete*	• Portal officially launched on November 30 and has continued to gain positive traction • The central call center has received a number of inquiries that have been directed to appropriate trials, resulting in many successful patient enrollments

Agent Prioritization Subgroup

The TX-Clinical WG continues to review agents for inclusion and prioritization in ACTIV studies. WG members are interested in ivermectin and fostamatinib and are contacting investigators from ongoing randomized controlled trials of these agents to inform prioritization decisions.

The WG has recently decided not to pursue (b) (4) [redacted] any further.

The green agents in the table below have been advanced to ACTIV studies; the blue agents have been advanced to other studies outside of ACTIV:

(b) (4) [redacted]

Discussion
ACTIV studies are collecting patient samples so that patients' SARS-CoV-2 variants can be genotyped, although this genotyping is not being conducted in real time.

Drs. Hughes and Read noted that the TX-Clinical WG has discussed ivermectin extensively, both because the most promising data on the compound were generated by smaller studies that are difficult to interpret, and because the agent's mechanism of action remains unknown. The WG will decide whether to accept this agent into ACTIV studies once it obtains additional RCT data.

The TX-Clinical WG has considered the possibility of launching an ACTIV-6 trial, envisioned to be a "low-touch" outpatient trial—possibly all remote—to study immune modulators and other agents such as ivermectin and fluvoxamine that may not fit well into existing ACTIV trials.

Vaccines WG

Doug Lowy, MD, NIH

During the previous Leadership Team meeting, Dr. Lowy presented a proposal for a multicomponent study of the impact of vaccination on duration/titers of viral shedding (placebo-controlled, in university students at multiple institutions, daily nasal swabs of participants, aggressive contact tracing). This proposed study is no longer being pursued because of concerns around feasibility, particularly related to the aggressive contract tracing component. The Vaccines WG is brainstorming alternative study designs that would provide valuable readouts but that would be simpler to execute. These discussions are ongoing.

Ongoing Phase III vaccine studies (e.g., Moderna and Novavax) contain sub-studies to assess asymptomatic viral shedding, which was a key component of the previously proposed study. Other studies will also be assessing the impact of vaccines on asymptomatic seroconversion. Observational studies of asymptomatic infection and shedding are also planned in the United States and the United Kingdom, which will assess seronegative healthcare/essential workers and investigate the impact of vaccination.

The Vaccines WG is also discussing ideas for studying allergic reactions that have been observed during introduction of mRNA vaccines against SARS-CoV-2. The WG is eager to see whether the protein-based SARS-CoV-2 vaccines cause similar reactions.

The Vaccines WG is also interested in identifying correlates of protection, which would enable rapid assessment of vaccine efficacy for new populations unrepresented in Phase III trials and accelerate development of second-generation vaccines. Objectives will be to identify an immune response shortly after vaccination that predicts clinical vaccine efficacy across vaccine products and platforms, and ideally to show that the correlate is causally linked to protection. The WG will leverage data from Phase III trials, complemented by natural history, passive immunization, and animal model study data. It will focus initially on antibody response correlates but will also explore cell-mediated immune response correlates. Preliminary data suggest that modest neutralizing antibody responses may be sufficient for vaccine efficacy, but much additional data are needed to establish Ab responses as a potential correlate.

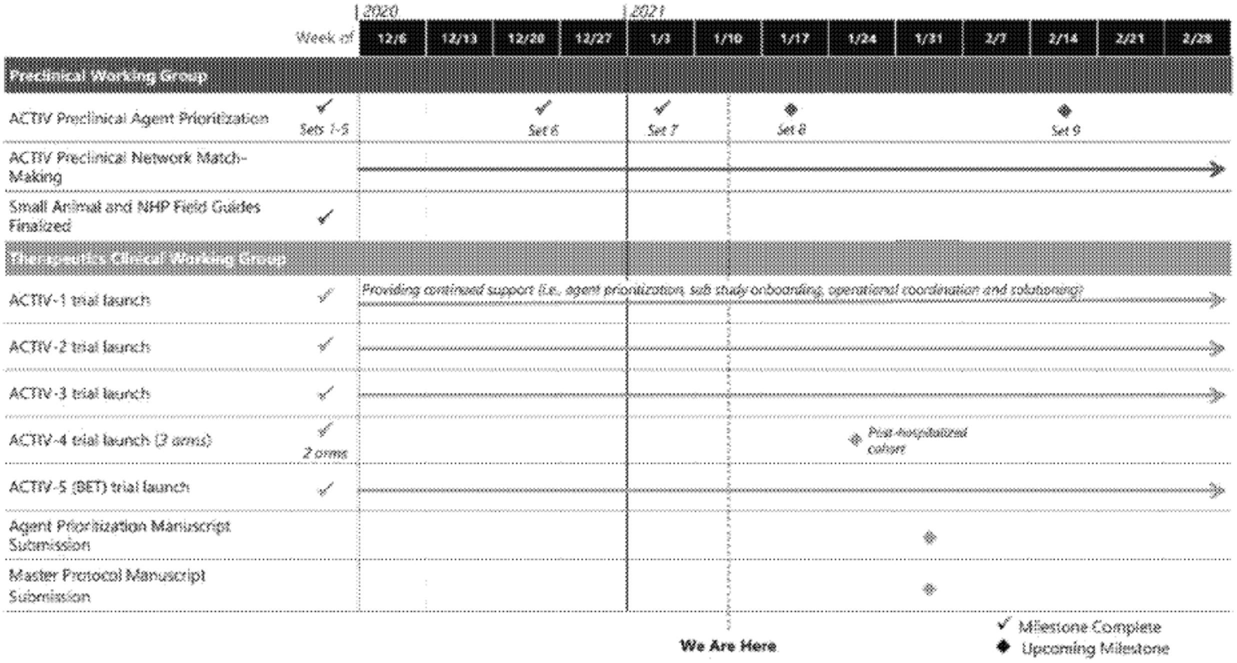
Discussion

Dr. Collins emphasized the importance of identifying correlates of protection to enable bridging studies; he conjectured that those patients who received either Pfizer/BioNTech's or Moderna's vaccine but were *not* protected from infection may be particularly valuable as subjects for these studies. Investigators must seek to understand *why* those individuals were not protected and to sequence the genomes of SARS-CoV-2 strains that infected them. Dr. Kathrin Jansen confirmed that Pfizer is already conducting some of this work (e.g., measuring neutralizing antibody titers and sequencing viral strains in recipients of the Pfizer vaccine), and expects initial results by mid-February. She also highlighted the importance (and the challenge) of analyzing T-cell responses to the viral antigen in vaccine recipients. Dr. Lowy added that it will be important to investigate potential differences in correlates of protection between mRNA- and protein-based vaccines.

Dr. Peter Marks emphasized the need to study vaccines' effects on asymptomatic transmission, referencing data from AstraZeneca's vaccine trial that appeared to show that vaccination might not reduce it, which has implications for the timeline for establishing herd immunity. Dr. (b)(6) [redacted] (b)(5) [redacted] but Dr (b)(6) [redacted] noted (b)(5) [redacted]

Adjourn

Dr. Collins closed the meeting by presenting the updated ACTIV milestones chart below:



The next two Leadership Team meetings will occur on February 17 and March 18, respectively.

Appendix A: Participants List

Francis Collins, MD, PhD, *Director, National Institutes of Health (NIH) (Session Co-Leader)*

James Anderson, MD, PhD, *Senior Investigator, National Heart, Lung, and Blood Institute (NHLBI)*

Kara Carter, PhD, *Senior VP Discovery Biology, Dewpoint Therapeutics*

Marco Cavaleri, *Head of Office, Anti-infectives and Vaccines, EMA*

Tomas Cihlar, PhD, *VP of Virology, Gilead Sciences*

Christine Colvis, PhD, *Director for Drug Development Partnership Programs, National Center for Advancing Translational Sciences (NCATS), NIH*

Larry Corey, MD, *President and Director Emeritus, Fred Hutchison Cancer Research Center*

Michelle Culp, MPH, *Office of the Director, NIH*

Victoria Davey, PHD, MPH, *Chief Research and Development Officer for Public Health and Epidemiology, US Department of Veterans Affairs*

Gary Disbrow, PhD, *Acting Director, Biomedical Advanced Research and Development Authority (BARDA)*

Emily Erbelding, MD, MPH, *Director, Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases (NIAID), NIH*

Stanley Erck, MBA, *President and CEO, Novavax*

Mark Esser, PhD, *Vice President, AstraZeneca*

Maria Freire, PhD, *President and Executive Director, FNIH*

Ellen Gadbois, PhD, *Program Lead, Emerging Biotechnology Policy, NIH Office of Science Policy*

Gary H. Gibbons, MD, *Director, NHLBI, NIH*

Adrienne Hallett, *Associate Director for Legislative Policy and Analysis, NIH*

Thomas J. Hudson, MD, *Vice President of Oncology Discovery and Early Development, AbbVie*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis*

Kathrin Jansen, PhD, *Senior Vice President, Head of Vaccine Research and Development, Pfizer*

Robert Johnson, PhD, *Director, Division of Influenza and Infectious Diseases, BARDA/ASPR/HHS*

H. Clifford Lane, MD, *Deputy Director for Clinical Research and Special Projects, NIAID*

Douglas Lowy, MD, *Principal Deputy Director, National Cancer Institute (NCI), NIH*

Peter Marks, PhD, *Director, Center for Biologics Evaluation and Research, FDA*

Hilary D. Marston, MD, MPH, *Medical Officer/Policy Advisor, NIAID, NIH*

John Mascola, MD, *Director, Vaccine Research Center, NIAID, NIH*

David Meeker, MD, *KSQ Therapeutics (formerly Genzyme)*

William Pao, PhD, MD, *Head, Pharma Research & Early Development, Roche/Genentech*

Ashley Parker, PhD, *Health Science Policy Analyst, NIH*

Roger M. Perlmutter, MD, PhD, *EVP and President, Merck Research Laboratories*

Andrew S. Plump, MD, PhD, *President, Research and Development, Takeda*

Mary Purucker, MD, PhD, *Director, Center for Translational Science Awards (CTSA), NCATS*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH*

Doris J. Rouse, PhD, *VP, Global Health Technologies, RTI International*
Daniel M. Skovronsky, MD, PhD, *Senior Vice President and Chief Scientific Officer, Eli Lilly and Co.*
Lawrence Tabak, DDS, PhD, *Principal Deputy Director, NIH*
John Tsai, MD, *Head, Global Drug Development and CMO, Novartis*
Rupert Vessey, DPhil, *President of Research and Early Development, Bristol-Meyers Squibb*
John Young, PhD, *Global Head, Infectious Diseases, Roche*
Carrie D. Wolinetz, PhD, *Associate Director for Science Policy, NIH*

Stacey Adam, PhD, *Director, Foundation for the NIH (FNIH)*
Stephanie James, PhD, *Senior VP of Science, FNIH*
Joseph P. Menetski, PhD, *Associate VP of Research Partnerships, FNIH*
Michael Santos, PhD, *Associate VP of Science, FNIH*
David Wholley, MPhil, *Senior VP of Research Partnerships, FNIH*

Evan Appell, *Consultant, Deloitte*
Helen Chen, PhD, *Manager, Deloitte*
Sarah Connelly, PhD, *Senior Consultant, Deloitte*
Nina Gonzalez, *Senior Manager, Deloitte*
Harrison Hawk, *Business Analyst, Deloitte*
Hana Nasr, *Consultant, Deloitte*
Alex David Sorosa, *Business Analyst, Deloitte*

Lucas Smalldon, MA, *Writer, Rose Li and Associates, Inc.*

Appendix B: Zoom Chat Transcript

10:42:14 From Vicky Davey to Everyone:

Is it still possible to nominate a scientist for one of the subteams? (from U.S. Department of Veterans Affairs)

10:43:54 From David Wholley to Everyone:

Sure, Vicky, please send the name and contact info to Joe Menetski.

10:44:20 From William Pao to Everyone:

Will there be an effort to do more systematic sequencing of patient samples across the US, e.g. in multiple centers? [Note: this was answered in the affirmative in the discussion]

10:44:48 From Gary Disbrow to Everyone:

Have you engaged DoD GEIS

10:49:11 From William Pao to Everyone:

Agree - this is incredibly important

11:26:19 From Emily Erbelding to Everyone:

all of the breakthrough infections will be sequenced in all Ph3 trials

High-Level Meeting Summary

The Leadership Team and Executive Committee ("Leadership Team") guiding the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) Partnership convened to review the status of current ACTIV efforts, presented by Co-Chairs of the Preclinical, Therapeutics Clinical (TX-Clinical), and Vaccines Working Groups (WGs).

Preclinical WG

John Young, PhD, Roche; Christine Colvis, PhD, NCATS

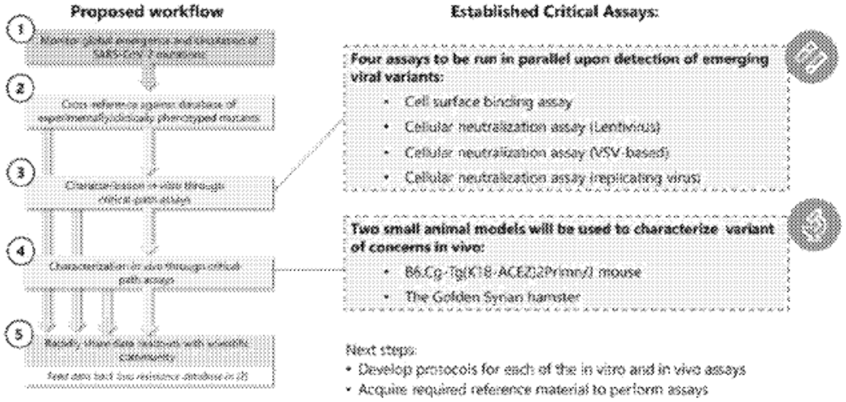
Agent Prioritization and Matchmaking

The Preclinical WG has completed its ninth round of preclinical agent prioritization and to date has evaluated 169 agents (18 since the Leadership Team's last meeting), 32 of which have been selected for matchmaking. The WG will conduct its tenth prioritization and matchmaking round on March 19, focusing especially on agents that have the potential to address long-term COVID-19 sequelae.

The TRACE WG

The Tracking Resistance and Coronavirus Evolution (TRACE) WG and its various subgroups have been developing processes and infrastructure for monitoring and testing emerging SARS-CoV-2 variants, as well as for standardizing, gathering, and sharing variant sequencing data. TRACE is currently working to (1) produce a weekly Viral Variant Report (2) develop assay overviews for the NCATS OpenData Portal, (3) detail critical path assays to characterize emerging variants, and (4) develop a plan to address conflicting assay-derived data.

Dr. Colvis presented the contents of the TRACE WG's weekly Viral Variant Report, encouraging Leadership Team members to submit any recommendations regarding further information these reports should include. She also noted that TRACE has developed assay overviews to describe its critical assays (i.e., how the assays work, their limitations, and how to interpret their results). Overviews have been drafted for pseudotype and live virus assays, and additional overviews for in vivo and other assays are being drafted now. The image below shows how the critical path assays will fit into the TRACE WG's overall proposed workflow:


Proposed workflow
① Monitor global emergence and circulation of SARS-CoV-2 mutations
② Cross reference against database of experimentally/clinically phenotyped mutants
③ Characterization in vitro through critical path assays
④ Characterization in vivo through critical path assays
⑤ Rapidly share data readouts with scientific community
Feed data back into resistance database in (2)
Established Critical Assays:

Four assays to be run in parallel upon detection of emerging viral variants:

- Cell surface binding assay
- Cellular neutralization assay (Lentivirus)
- Cellular neutralization assay (VSV-based)
- Cellular neutralization assay (replicating virus)

Two small animal models will be used to characterize variant of concerns in vivo:

- B6.Cg-Tg(K18-ACE2)2Prlmn/J mouse
- The Golden Syrian hamster

Next steps:

- Develop protocols for each of the in vitro and in vivo assays
- Acquire required reference material to perform assays

Discussion
Dr. Rajeev Venkayya suggested that the TRACE WG develop a strategy to prioritize sequencing of SARS-CoV-2 strains from cases of vaccine breakthrough, and Dr. Paul Stoffels stressed the need to coordinate across the globe to sequence and share data from such strains as soon after their emergence as possible. Dr. Venkayya recommended that CDC issue guidance to state laboratories to prioritize breakthrough strains for sequencing and data sharing, noting that WHO could release similar guidance to achieve global coordination. Dr. Collins will follow up with CDC on this as well as the need for surveillance efforts to adequately monitor infections in populations of particular concern, such as underserved minorities and the immunocompomised (an issue discussed later in the meeting).

Dr. Francis Collins confirmed that ACTIV has yet to gain access to GISAID's viral sequencing data, although he and others have proposed to GISAID a modification of its data access policy to lower barriers. Dr. William Pao noted that, if that proposal is rejected, ACTIV could engage top journal editors to convince GISAID that data sharing is critical to address the pandemic. Dr. Collins acknowledged the suggestion but is hopeful that current discussions will be productive.

Therapeutics-Clinical WG

Sarah Read, MD, NIAID; Eric Hughes, MD, PhD Novartis

Drs. Read and Hughes provided updates on the TX-Clinical WG's Master Protocol Subgroup and Agent Prioritization Subgroup. Dr. Hughes also noted that the WG's Clinical Manuscript Subteams have developed two sister manuscripts documenting the strategy, process, and lessons learned from agent prioritization and master protocol development, and that both of these manuscripts have been submitted to *Annals of Internal Medicine*.

Master Protocol Subgroup

Dr. Read summarized the status, as of March 17, of ACTIV's master protocols:

- **ACTIV-1:** phase III; immune modulators; inpatients
    - **Status:** 54 sites (6+ satellite sites) and 518 participants; activating additional sites, including in Peru, Argentina, Brazil, Mexico; submitted response on protocol amendment and statistical analysis plan to FDA on March 1; expect to have enough data for first interim futility analysis during April (DSMB meeting scheduled for early May)
    - **Sponsor:** Duke Clinical Research Institute (DCRI) + NCATS Trial Innovation Network (TIN) + TRI
    - **First agents**: abatacept, infliximab, cenicriviroc
- **ACTIV-2:** phase II/III; neutralizing antibodies (nAbs) and oral antivirals; outpatients
    - **Status:** 132 sites and (b) (4) ; onboarding new sites; study team working to incorporate into the trial design an active control for high-risk participants
        - Phase II–(b) (4) : (b) (4) ; (b) (4) ; (b) (4) ; (b) (4) : (b) (4) led; (b) (4) : (b) (4)
        - Phase III—(b) (4) : (b) (4)

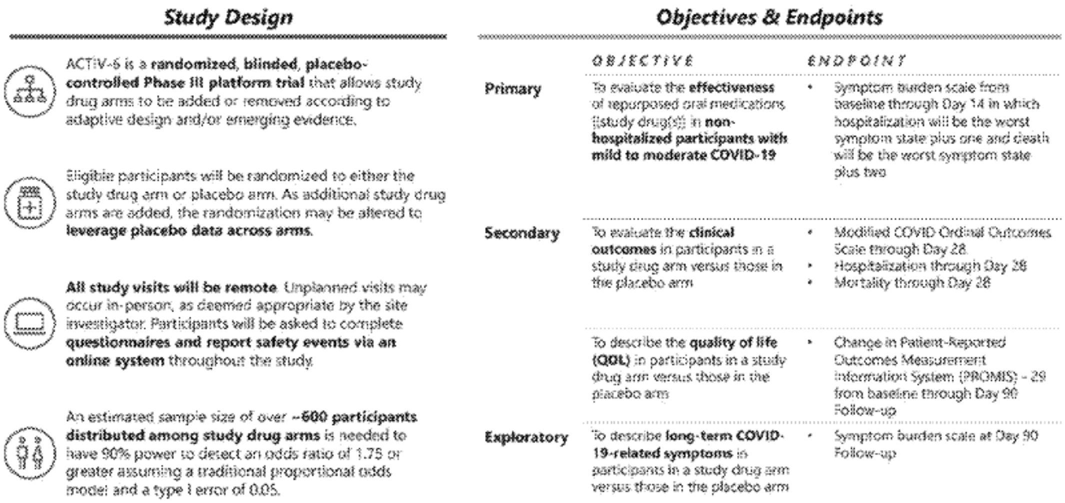
  - **Sponsor:** NIAID AIDS Clinical Trials Group (ACTG) + CRO
  - **Future agents:** nAb from RU-BMS and polyclonal antibody from SAB
- **ACTIV-3:** phase II/III (will include phase I testing option for agents that need it); neutralizing monoclonal nAbs; inpatients
  - **Status:** 61 sites and (b) (4)
    - (b) (4): (b) (4) (closed, patient numbers not included in total above); (b) (4): (b) (4); (b) (4): (b) (4)
    - ACTIV-3b/TESICO protocol studying aviptadil in severely ill patients received "safe to proceed" from FDA on March 12
  - **Sponsor:** NIAID INSIGHT + NHLBI PETAL + NHLBI CTSN + VA + CRO
  - **Future agents**: nAbs from (b) (4), and DARPin from (b) (4)
- **ACTIV-4:** phase III; anticoagulants; inpatients (cohorts: pre-hospitalized, hospitalized, post-hospitalized)
  - **Status:**
    - Hospitalized: 61 sites and (b) (4); patient enrollment has re-started following paused to incorporate evaluation of anti-platelet agents into the protocol.
    - Pre-hospitalized: 41 sites and (b) (4)
    - Post-hospitalized: 3 sites activated, (b) (4)
  - **Sponsor:** NHLBI-NINDS CONNECTS Network
  - **First agents:** hospitalized: low molecular weight heparin, unfractionated heparin, and P2Y12 inhibitors; pre-hospitalized: aspirin, low/high dose apixaban; post-hospitalized: apixaban
- **ACTIV-5:** phase II; proof of concept study to identify promising treatments; inpatients
  - **Status:** 19 sites and (b) (4); prioritizing additional agents
  - **Sponsor:** NIAID + IDCRC + Leidos
  - **First agents:** risankizumab and lenzilumab

ACTIV-3 DSMB Decision on (b) (4)

The ACTIV-3 DSMB reviewed data on 344 people in the (b) (4) and 342 people in the (b) (4) combination sub-study and provided written comments on March 1. The DSMB analysis determined that the (b) (4) cocktail did not meet the inclusion criteria for further enrollment in the trial, due to futility. The DSMB's initial analysis of data from the (b) (4) sub-study indicated that the treatment met pre-specified criteria for study continuation. However, participants entering the control group had more advanced illness overall than those entering the therapeutic group; once statistical adjustments were applied to account for this imbalance, the DSMB recommended halting enrollment for (b) (4). The DSMB recorded no safety concerns for either (b) (4) therapeutic agents. Patients from both sub-studies will be followed for 18 months, and ACTIV-3 will develop a preliminary report once the 5-day follow up for all patients has been completed.

Pragmatic Platform Trial (ACTIV-6): Protocol Overview

Dr. Read presented an overview of the ACTIV-6 remote pragmatic platform trial, shown below:



Study Design

ACTIV-6 is a **randomized, blinded, placebo-controlled Phase III platform trial** that allows study drug arms to be added or removed according to adaptive design and/or emerging evidence.

Eligible participants will be randomized to either the study drug arm or placebo arm. As additional study drug arms are added, the randomization may be altered to **leverage placebo data across arms**.

All study visits will be remote. Unplanned visits may occur in-person, as deemed appropriate by the site investigator. Participants will be asked to complete **questionnaires and report safety events via an online system** throughout the study.

An estimated sample size of over **~600 participants distributed among study drug arms** is needed to have 90% power to detect an odds ratio of 1.75 or greater assuming a traditional proportional odds model and a type I error of 0.05.

Objectives & Endpoints

	OBJECTIVE	ENDPOINT
Primary	To evaluate the **effectiveness** of repurposed oral medications [study drug(s)] in **non-hospitalized participants with mild to moderate COVID-19**	• Symptom burden scale from baseline through Day 14 in which hospitalization will be the worst symptom state plus one and death will be the worst symptom state plus two
Secondary	To evaluate the **clinical outcomes** in participants in a study drug arm versus those in the placebo arm	• Modified COVID Ordinal Outcomes Scale through Day 28 • Hospitalization through Day 28 • Mortality through Day 28
	To describe the **quality of life (QOL)** in participants in a study drug arm versus those in the placebo arm	• Change in Patient-Reported Outcomes Measurement Information System (PROMIS) - 29 from baseline through Day 90 Follow-up
Exploratory	To describe **long-term COVID-19-related symptoms** in participants in a study drug arm versus those in the placebo arm	• Symptom burden scale at Day 90 Follow-up

Ivermectin is currently slated to be the first agent tested in ACTIV-6; further agent prioritization will soon begin.

Agent Prioritization Subgroup

Following recent discussions with the ACTIV Leadership Team and given that most ACTIV trials are approaching capacity for onboarding new agents, ACTIV will pause most agent prioritization efforts. Reviews of agents currently under consideration will be completed, but the TX-Clinical WG will inform new agent submitters that ACTIV trials have reached capacity and that their agents will be considered only if space becomes available in one of the trials. (This pause will not apply to ACTIV-6.)

Considering the Impact of Variants and Vaccines on Therapeutics

As the pandemic continues to evolve, ACTIV's clinical trial teams have made several adjustments to both trial designs and agent prioritization criteria in order to proactively address issues regarding emerging viral variants and the implications of vaccination:

- Revised neutralizing Ab criteria to favor nAb cocktails over single agents following the relatively weak readouts from recent single-agent trials.
- Began requiring variant data for all new nAb (and antiviral) agent submissions in order to evaluate efficacy against emerging and currently circulating virus.
- Planned two studies on the impact of vaccines post-mAb treatment. The ACTIV-2/-3 trials are attempting to obtain approximately 1,000 vaccine doses per study.

Discussion

Dr. Pao proposed pooling data from the monoclonal Ab studies that have passed through ACTIV inpatient master protocols to determine whether any subset of patients shows signs of benefit across the larger comparative dataset. Drs. Hughes and Read endorsed Dr. Pao's proposal, and Dr. Janet Woodcock noted that the (b) (4) trial is beginning to test (b) (4) monoclonal Ab and that those data could be included in a pooled comparative dataset for monoclonal Abs. Dr. Read also expressed interest in seeing whether (b) (4) provides benefit as well.

Dr. Gary Gibbons expressed concern that ACTIV inpatient master protocols (ACTIV-1/-3/-4) may not be pivoting rapidly enough away from monoclonal Abs toward host-targeted therapies, which may be more effective against severe COVID-19. Dr. Hughes noted that it is difficult for antiviral agents to act in the later stages of disease. Dr. Read emphasized that ACTIV-3b will evaluate aviptadil in severe cases, adding that few agents that target patients with severe disease that have sufficient data to support clinical development have been submitted to ACTIV.

Vaccines WG

Doug Lowy, MD, NIH; Michael Santos, PhD, FNIH

The Vaccines WG has spent its last five meetings discussing viral variants and their implications for vaccine development and use. During the past 6 months, substantially evolved variants have emerged and spread regionally. Vaccination and pre-existing immunity protect less well against infection and mild disease caused by some of these variants, and the variants with the most concerning resistance mutations are becoming locally prevalent in parts of the United States. These developments are concerning for the following reasons:

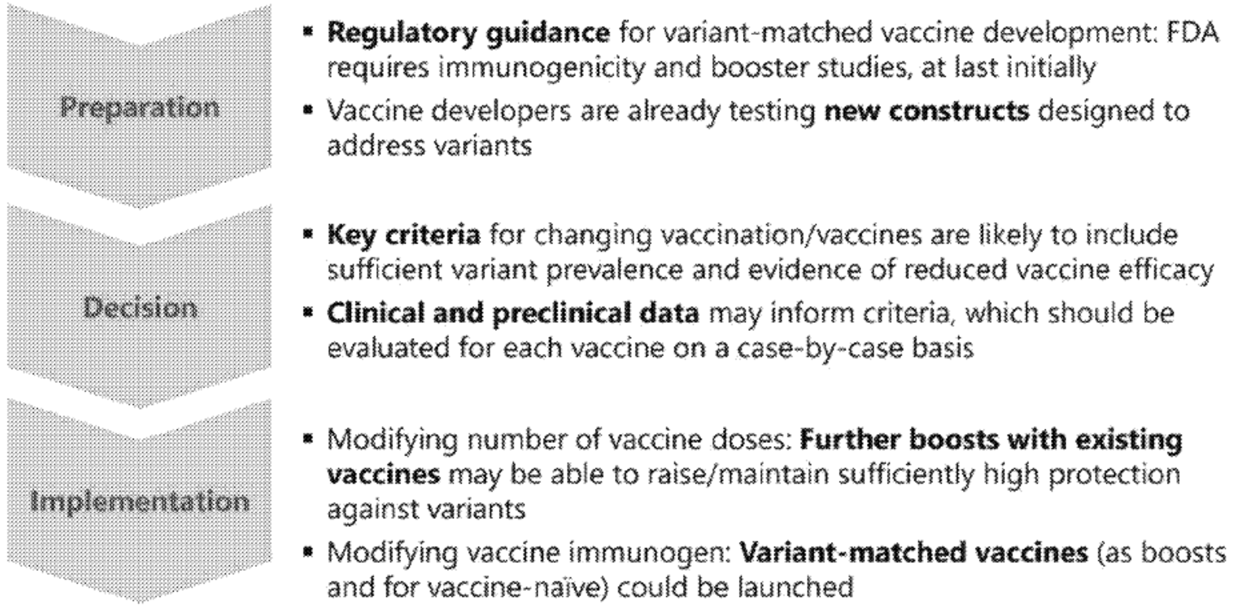
1. Variants may increase the difficulty of reaching herd immunity in a population.
2. Changes to vaccination (e.g., extra boost) or vaccines (variant-matched additions) may be needed to increase protection against variants.
3. The U.S. COVID-19 health burden in winter 2021-2022 is highly uncertain, and a key question is how well current vaccines and natural immunity will protect against risks of variant-related hospitalization and death.

Some researchers have proposed that the variants of most concern, such as the UK, South Africa, and Brazil variants, may have evolved in individual immunocompromised patients with chronic infections, which raises important questions about diagnosis, treatment, and transmission prevention for these populations.

The variants of most concern also exhibit certain shared mutations (e.g., the E484K mutation in the receptor binding domain), which imply instances of convergent evolution toward increased infectivity or escape from natural immunity. Available data indicate that both vaccination and natural immunity show reduced prevention of infection/mild disease and neutralization against the South Africa variant, which has the E484K mutation, than they show against other circulating SARS-CoV-2 strains. More data are being generated about more serious outcomes, such as hospitalization and death.

Dr. Santos showed that the prevalence of E484K variants in New York City is increasing rapidly, and that immunity against these variants will be important for U.S. epidemiology in 2021. He shared that plausible epidemiological scenarios for winter 2021-2022 range from herd immunity to a large surge in new cases, depending on factors such as the rate of spread of the variants, the cross-variant protection of vaccination and natural immunity, the rate of behavior change (e.g., mask wearing and social distancing), and vaccine coverage (e.g., among children).

Dr. Lowy presented the graphic below, which addresses regulatory implications of the points outlined above, and Dr. Woodcock stressed that much uncertainty remains for regulators.



Preparation

- **Regulatory guidance** for variant-matched vaccine development: FDA requires immunogenicity and booster studies, at last initially
- Vaccine developers are already testing **new constructs** designed to address variants

Decision

- **Key criteria** for changing vaccination/vaccines are likely to include sufficient variant prevalence and evidence of reduced vaccine efficacy
- **Clinical and preclinical data** may inform criteria, which should be evaluated for each vaccine on a case-by-case basis

Implementation

- Modifying number of vaccine doses: **Further boosts with existing vaccines** may be able to raise/maintain sufficiently high protection against variants
- Modifying vaccine immunogen: **Variant-matched vaccines** (as boosts and for vaccine-naïve) could be launched

Discussion
Dr. Venkayya noted that Operation Warp Speed (OWS) previously committed to analyzing correlates of protection across all OWS-funded programs using a standard, validated assay, and other participants confirmed that the results of those analyses should be available by mid-April for both Pfizer and Moderna. Dr. Stoffels stressed the importance of moving quickly to begin developing and testing vaccines against the variants of most concern in light of how quickly some of them appear to spread.

Dr. Roger Perlmutter noted that, although new variants might infect individuals who were previously infected with an earlier strain, these infections may not cause serious illness if the infected individuals have sufficient memory responses that recognize and respond rapidly to the pathogen. Consequently, it may be difficult to use information on circulating neutralizing antibody titers to identify correlates of protection. Dr. Perlmutter noted that identifying such correlates will likely require longer-term population studies focused on previously vaccinated individuals who may become infected many months after vaccination.

Dr. Mikael Dolsten emphasized the need to track the timeline of post-vaccination neutralizing Ab titers and to compare it to the titers necessary for protection; this comparison will be crucial for informing appropriate timing of vaccine boosting.

Dr. Collins asked whether the Vaccines WG has discussed what infection strategies SARS-CoV-2 might evolve in the future, and whether programs to proactively develop vaccines against such strategies could be initiated. Dr. Lowy noted that the Vaccines WG has received a presentation from Dr. Jesse Bloom showing that the E484K mutation was the most concerning, but new mutations could arise under pressure from vaccine-induced immunity. Dr. Dolsten raised the possibility of administering vaccine boosts that are matched to specific mutations of concern, such as E484K, or pursuing other strategies for amplifying the post-vaccination production of lymphocyte clones to fight a broader range of strains that might subsequently infect the body.

Dr. Gibbons highlighted the importance of achieving granular and widespread surveillance of new infections so that populations of particular concern (e.g., immunocompromised patients) can be adequately monitored and recruited into studies to test new vaccination strategies. Dr. Collins agreed, and said he would follow this point up as part of discussions he is planning to have with CDC mentioned above.

In response to a comment from Dr. Dolsten, Dr. Collins also emphasized that NIH is conducting intensive studies of post-acute COVID-19 sequelae but added that the data are presently hard to interpret because investigators lack a clear criterion to classify a patient as having so-called “long COVID.”

Adjourn

The next two Leadership Team meetings will occur on April 28 and May 28, respectively.

Appendix A: Participants List

Francis Collins, MD, PhD, *Director, National Institutes of Health (NIH) (Session Co-Leader)*

Paul Stoffels, MD, *Vice Chairman of the Executive Committee and Chief Scientific Officer, Johnson & Johnson (Session Co-Leader)*

James Anderson, MD, PhD, *Senior Investigator, National Heart, Lung, and Blood Institute (NHLBI)*

Kara Carter, PhD, *Executive VP Infectious Disease, Evotec*

Tomas Cihlar, PhD, *VP of Virology, Gilead Sciences*

Christine Colvis, PhD, *Director for Drug Development Partnership Programs, National Center for Advancing Translational Sciences (NCATS), NIH*

Larry Corey, MD, *President and Director Emeritus, Fred Hutchison Cancer Research Center*

Victoria Davey, PHD, MPH, *Chief Research and Development Officer for Public Health and Epidemiology, US Department of Veterans Affairs*

Gary Disbrow, PhD, *Acting Director, Biomedical Advanced Research and Development Authority (BARDA)*

Mikael Dolsten, MD, PhD, *CSO and President, Worldwide R & D, Pfizer*

Maria Freire, PhD, *President and Executive Director, FNIH*

Ellen Gadbois, PhD, *Program Lead, Emerging Biotechnology Policy, NIH Office of Science Policy*

Gary H. Gibbons, MD, *Director, NHLBI, NIH*

Sarah Grant, MD, *Strategic Assistant to Head Global Drug Development, Novartis*

Thomas J. Hudson, MD, *Vice President of Oncology Discovery and Early Development, AbbVie*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis*

H. Clifford Lane, MD, *Deputy Director for Clinical Research and Special Projects, NIAID*

John Lepore, PhD, *Senior Vice President, Government Engagement, Moderna*

Douglas Lowy, MD, *Principal Deputy Director, National Cancer Institute (NCI), NIH*

David Meeker, MD, *KSQ Therapeutics (formerly Genzyme)*

Hitesh Pandaya, MD, *Medical Science Director, AstraZeneca*

William Pao, PhD, MD, *Head, Pharma Research & Early Development, Roche/Genentech*

Ashley Parker-Gordon, PhD, *Health Science Policy Analyst, NIH*

Roger M. Perlmutter, MD, PhD, *EVP and President, Merck Research Laboratories*

Kim D. Pruitt, PhD, *Chief, Information Engineering Branch, National Center for Biotechnology Information (NCBI), National Library of Medicine*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH*

David Reese, MD, *Executive Vice President Research & Development, Amgen*

Doris J. Rouse, PhD, *VP, Global Health Technologies, RTI International*

Stephen Sherry, PhD, *Acting Director, NCBI, NIH*

Rajeev Venkayya, MD, *President, Global Vaccine Business Unit, Takeda*

Carrie D. Wolinetz, PhD, *Associate Director for Science Policy, NIH*

Janet Woodcock, MD, *Acting Commissioner, FDA*
John Young, PhD, *Global Head, Infectious Diseases, Roche*

Joseph P. Menetski, PhD, *Associate VP of Research Partnerships, FNIH*
Michael Santos, PhD, *Associate VP of Science, FNIH*
David Wholley, MPhil, *Senior VP of Research Partnerships, FNIH*

Margaret Anderson, MA, *Managing Director, Deloitte*
Evan Appell, *Consultant, Deloitte*
Helen Q. Chen, PhD, *Manager, Deloitte*
Sarah Connelly, PhD, *Senior Consultant, Deloitte*
Nina Gonzalez*, Senior Manager, Deloitte*
Harrison Hawk, *Business Analyst, Deloitte*
Stephanie James, PhD, *Senior VP of Science, FNIH*
Serena Melton, *Senior Consultant, Deloitte*
Hana Nasr, *Consultant, Deloitte*

Lucas Smalldon, MA, *Writer, Rose Li and Associates, Inc.*

High-Level Meeting Summary

Representatives of all ACTIV trial teams convened to receive trial status updates, hear a presentation on best practices of site activation and recruitment, and discuss two pressing topics: an ACTIV-3 co-enrollment proposal that might be a potential template for other trials if the regulatory agencies will support it and the implications of (b) (4) trials for all the relevant ACTIV trials.

Action Items

- Col. Deydre Teyhen will explore whether OWS can develop turnkey press releases to help trials leverage major events for media outreach and patient enrollment.
- Dr. Stacey Adam will share trial team ideas regarding patient enrollment with ACTIV and OWS leadership for further discussion.

Trial Status Updates

ACTIV-1

ACTIV-1 expects to receive a response to its IND and to have its first fully-activated sites during the week of September 28. After encountering some drug availability issues, the trial team has arranged for supply from two of three companies over the next week and, with that supply, will be able to launch during the first week of October.

ACTIV-2

ACTIV-2 has recently increased patient enrollment. Based on the interim results of (b) (4) study, the trial team is preparing to move from a 7,000 to 700 mg dose of its agent, with work in process to finalize a revised appendix that will be submitted to FDA during the week of October 5. ACTIV-2 will continue high-dose enrollment until this transition is complete.

ACTIV-3

ACTIV-3 has (b) (4)s and opened 36 sites (including its first international sites), with additional activated sites awaiting drug supply. The trial team is exploring the interim results of the (b) (4) trial but is not considering a dose change at this time.

ACTIV-4

ACTIV-4A has activated three sites and (b) (4). It hopes to open its first international site in Spain during the next several weeks but has lost approximately 40 identified sites in Brazil, where the virus is now well controlled and few patients test positive.

ACTIV-4B opened for enrollment two weeks ago and has one site screening and one approaching launch. It ultimately needs 250 to 300 sites to reach its target of 7,000 patients.

ACTIV-4C has finalized its protocol and is preparing its IRB and IND for submission. The trial team is also monitoring ACTIV-4A and -4B sites to leverage them once it receives approval.

ACTIV-5

ACTIV-5 has received IRB approval and is waiting for FDA approval of a protocol amendment to be submitted on September 25. The trial will likely begin during the next two weeks.

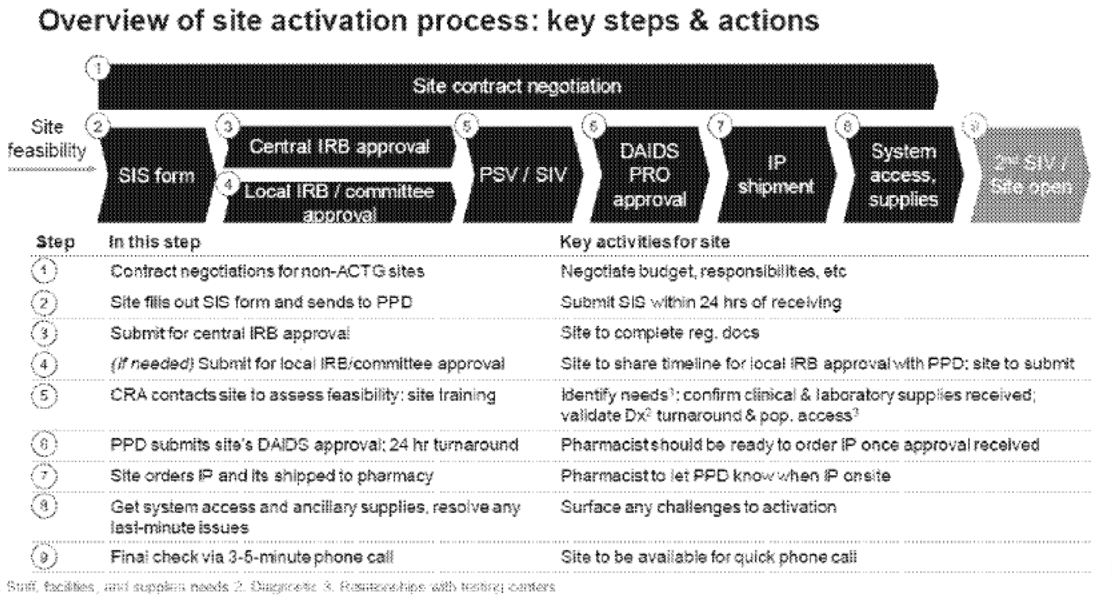
Discussion

Dr. Lisa LaVange emphasized the importance of consistent endpoints across ACTIV trials and encouraged ACTIV-5 to make a case for that consistency in its dialogue with FDA. The ACTIV-5 team understands that it can enlist Dr. Peter Stein for assistance with that dialogue if needed.

Best Practices: ACTIV-2 Site Activation and Enrollment

Davey Smith, MD (ACTIV-2)

The ACTIV-2 team has created an "activation playbook" that synthesizes what it has learned of best practices for site activation and enrollment during COVID-19. Dr. Smith suggested that the first key lesson of ACTIV-2 is the importance of *sharing* this playbook with sites early in the activation process. He then highlighted key learnings in particular areas.



Overview of site activation process: key steps & actions

Step	In this step	Key activities for site
①	Contract negotiations for non-ACTG sites	Negotiate budget, responsibilities, etc
②	Site fills out SIS form and sends to PPD	Submit SIS within 24 hrs of receiving
③	Submit for central IRB approval	Site to complete reg. docs
④	*(If needed)* Submit for local IRB/committee approval	Site to share timeline for local IRB approval with PPD; site to submit
⑤	CRA contacts site to assess feasibility; site training	Identify needs^{1}; confirm clinical & laboratory supplies received; validate Dx^{2} turnaround & pop. access^{3}
⑥	PPD submits site's DAIDS approval; 24 hr turnaround	Pharmacist should be ready to order IP once approval received
⑦	Site orders IP and its shipped to pharmacy	Pharmacist to let PPD know when IP onsite
⑧	Get system access and ancillary supplies, resolve any last-minute issues	Surface any challenges to activation
⑨	Final check via 3-5-minute phone call	Site to be available for quick phone call

1. Staff, facilities, and supplies needs 2. Diagnostic 3. Relationships with testing centers

Site activation: Teams should plan to conduct site-specific needs assessments, which can be completed in a single phone call, to pinpoint obstacles that sites may not otherwise identify. ACTIV-2 assessments revealed the importance of accelerating regulatory review at the local and national levels as well as helping sites navigate unfamiliar CRO terminology.

Patient enrollment: Sites should apply for HIPAA waivers that allow them to directly contact people who have tested positive. However, trial teams also need to help sites establish a broader patient identification and engagement "funnel" that ranges from marketing plans to adequate point-of-care staffing. A broad range of site staff—including but not limited to PIs—should be engaged in marketing outreach to local media and referral centers; a two-week concentrated PR effort can leverage media interest in COVID-19 to accelerate recruitment.

Communication: Communication can pose as significant a barrier as logistics. Trial teams should encourage sites to prioritize communication with their CRO, but should not assume sites will proactively convey their needs; instead, teams should take the initiative to solicit information about obstacles so they can be removed (e.g., obtaining infusion pumps or adding nurses).

Regulatory process: Sites should be encouraged to request a waiver of local IRB review or an expedited review if a waiver is unavailable; teams should also help sites avoid late changes to regulatory documents that would trigger an IRB resubmission. Beyond formal regulatory processes, teams should also anticipate some reluctance from hospital administrators who may be concerned that COVID-19 patients will discourage visits from other patients. ACTIV-2 found that a letter from Francis Collins helped reassure IRBs and some hospital administrators.

Streamlining participation: Sites should proactively facilitate patient participation by adopting flexible infusion hours and ensuring a skilled technician is performing infusions.

Discussion

Col. Deydre Teyhen emphasized the importance of leveraging major events, such as (b) (4) press release, to promote media attention and thus patient enrollment. OWS may help by developing turnkey press releases, with a quote that can be attributed to each study's PI prior to local media distribution. Col. Teyhen also encouraged trial teams to adopt a "concierge" approach to site engagement by designating a point person charged with connecting sites to OWS' own highly tailored logistical support (e.g., its capacity to build mobile units for hospitals concerned about serving COVID-19 outpatients).

ACTIV-3 Co-Enrollment Proposal

Jens Lundgren, MD and Jim Neaton, MD (ACTIV-3)

The original protocol for ACTIV-3 (also known as TICO) required patients not to participate in another trial until after Day 5, with an exception for life-threatening disease and end-organ failure. The trial team is preparing a protocol amendment that will significantly broaden co-enrollment. The proposed amendment leverages ACTIV-3's combination of investigational agent *plus Standard of Care (SOC)* to permit co-enrollment with trials that apply SOC interventions in varying ways (e.g., various doses of glucocorticoid, different target O_2 saturation levels). Randomized assignment of ACTIV-3 patients to these SOC applications will reduce bias in ACTIV-3 and create randomized controlled trials of therapies that are currently being routinely administered outside of trial settings—thus helping to refine SOC further.

The trial team has developed seven principles (below) to govern selection of co-enrolling trials. These principles aim to bar the possibility of testing two investigational agents simultaneously and thus to prevent any interpretive confusion that might arise in interpreting adverse events.

1. Applicable trials should **not** address a research question of whether the intervention should be applied or not, but rather how to apply it (e.g., dose, intensity, duration).
2. The target population must be patients in whom the intervention is commonly applied as part of SOC.
3. The trial intervention should be outlined in appendix I, Standard of Care, and hence viewed already as part of appropriate SOC by the TICO trial.
4. Interventions that are contraindicated in combination with the investigational agent are not permitted (see appendix H for details of possible contraindications for each investigational agent).
5. Study procedures of the co-enrolling trial must not impose an undue burden on research participants when viewed within the context of the TICO study procedures. For example, volume of blood drawn for research purposes must not be excessive when added to the volume drawn for TICO study procedures.
6. Participation in the TICO trial is the principal trial for the study participant, and TICO study procedures should be prioritised.
7. The trial must be open-label (non-blinded) in order to facilitate interim and final analyses of TICO data, including treatment interactions, and the attribution of causality of serious adverse events and unanticipated problems (see section 10.1.5.)

This proposal has received informal feedback from FDA staff and will be formally submitted when another agent is added to the ACTIV-3 protocol (within the next several weeks). ACTIV-3 is also pursuing discussions with potential partner trials, beginning with ACTIV-4 (50% of enrollees are expected to come from ex-U.S. sites, so other trial partners will also be explored).

Discussion

Participants agreed that the co-enrollment proposal is well designed and will accelerate evidence gathering. However, they debated the extent to which co-enrollment can overcome the overall low number of patients enrolled in COVID-19 trials.

Dr. Lundgren noted that to the extent that competition for patients is driving low enrollment, co-enrollment will help alleviate the problem. During the ACTIV-3 site survey, such competition was indeed perceived by PIs as a contributor to enrollment challenges. However, Dr. Paul Ridker suggested that co-enrollment poses a different potential problem: it asks a small number of sites to manage a large number of trials, and thus risks inadequate site resources. Participants discussed several other approaches to the broader COVID-19 enrollment challenge:

- High-level leadership might remove competition for patients by encouraging a formal (e.g., geographic) division that clearly divides different trials across distinct spaces.
- Because the existence of multiple protocols creates competition, a shared randomization that cuts across the protocols could alleviate the problem: patients could be randomly assigned to any protocol, limited only by inpatient or outpatient status, rather than be recruited first and randomly assigned (to a trial arm) second.
- ACTIV may significantly expand engagement of non-academic locations (e.g., community hospitals) to broaden the pool of potential trial participants.
- ACTIV leadership may establish consensus regarding which of its trials should be prioritized in the near term, even at the expense of enrollment in others.

Participants recognized that these ideas require broader assessment and discussion by ACTIV and OWS leadership.

(b) (4) [redacted] and (b) (4) [redacted] Implications

John Beigel, PhD (ACTIV-5)

Dr. John Beigel presented an overview of ACTT-2's recently completed trial of (b) (4) [redacted]. ACTT-2 (b) (4) [redacted] at 67 sites over 54 days (from the beginning May through the end of June, with follow-up through end of July). Patients' baseline condition was rated on an 8-point ordinal scale, and investigators then used that scale to assess the primary endpoint of time to recovery and the secondary endpoint of condition on day 15. Overall, patients receiving (b) (4) [redacted] exhibited better outcomes than those receiving placebo: the experimental group had an average 7-day recovery (compared to 8 days for placebo; p=.03), an odds ratio of 1.3 for improved condition on day 15 (p=.03), and a mortality hazard ratio of .65 (p=.09).

ACTT-2 was not designed to compare patients with different baseline scores, but it did reveal intriguing distinctions across these categories. Patients requiring high-flow oxygen exhibited generally stronger effects, with an average 10-day recovery (versus 18 days on placebo), an improvement odds ratio of 2.3, and a mortality hazard ratio of .55 (those receiving low-flow oxygen had a mortality hazard ratio of .4). People not on oxygen gained no benefit from (b) (4) [redacted] and in some cases had a slower recovery than patients receiving placebo.

These results tentatively suggest that (b) (4) [redacted] and (b) (4) [redacted] may work best in complementary populations (with the latter helping ventilated patients). However, the very different designs of ACTT-2 and the (b) (4) [redacted] Y trial of (b) (4) [redacted] (which was unblinded and had very few exclusions) make it difficult to draw a conclusion. The study team is meeting with NIH staff to discuss whether (b) (4) [redacted] should become part of SOC.

Discussion

Drs. (b) (6) [redacted] and (b) (6) [redacted] emphasized that ACTT-2 (b) (5) [redacted]. Dr. (b) (6) [redacted] suggested that (b) (5) [redacted] (b) (4) [redacted] trial; she noted that (b) (5) [redacted]

Dr. (b) (6) [redacted] clarified (b) (5) [redacted]. The trial team is (b) (5) [redacted]. The team is also (b) (5) [redacted]

Dr. (b) (6) [redacted] noted (b) (5) [redacted]

Next Meetings

At upcoming Cross-Trial Meetings, participants will hear an overview of ACTIV-5 (BET); discuss opportunities for merging data, integrating screening and recruitment across ACTIV trials, and influencing clinical practice; and review ACTIV resources (including site needs assessment tools and solutions, endpoints and inclusion/exclusion criteria cross-walk, clinical trial capacity dashboard, and accrual simulation model). Trial team members may contact Dr. Adam to nominate other topics for discussion or request any other coordination beyond these meetings.

Appendix A: Participants List

TRIAL TEAM MEMBERS

ACTIV-1

William G. Powderly, MD, *ACTIV-1 Chair and J. William Campbell Professor of Medicine, Director of the Institute for Clinical and Translational Sciences, Washington University in St. Louis*

Lisa LaVange, PhD, *Professor and Associate Chair, Department of Biostatistics, UNC Chapel Hill*

Michael Proschan, PhD, *Mathematical Statistician, Biostatistics Research Branch, National Institute of Allergy and Infectious Diseases (NIAID), NIH*

ACTIV-2

David (Davey) Smith, MD, *ACTIV-2 Chair Professor of Medicine, U. California, San Diego*

Judith Currier, MD, (not in attendance) *Professor of Medicine in the Division of Infectious Diseases, University of California, Los Angeles (UCLA)*

Peter Kim, MD, *Director, Therapeutics Research Program, Division of AIDS, NIAID*

ACTIV-3

James D. Neaton, PhD, *ACTIV-3 Chair and Professor of Biostatistics, University of Minnesota*

Jens D. Lundgren, MD, *Professor of Viral Diseases, University of Copenhagen*

Birgit Grund, PhD, *Associate Professor of Statistics, University of Minnesota*

ACTIV-4

Judith S. Hochman, MD, *ACTIV-4A Chair and Harold Snyder Family Professor of Cardiology, Department of Medicine, NYU Grossman School of Medicine*

Paul Ridker, MD, *ACTIV-4B Chair; Senior Physician, Brigham and Women's Hospital; Eugene Braunwald Professor of Medicine, Harvard Medical School*

Tom Ortel, MD, PhD, *ACTIV-4C Chair and Chief, Division of Hematology, Department of Medicine, Duke University*

Scott Berry, PhD, *Adjunct Professor, Department of Biostatistics & Data Science, Kansas University Medical Center*

Andrei Kindzelski, MD, PhD, *Program Director, Division of Blood Diseases and Resources, NHLBI, NIH*

Eric Leifer, PhD, *Mathematical Statistician, NHLBI, NIH*

Allison Morris, MD, *ACTIV-4D Co-Chair and Professor of Medicine, Immunology, and Clinical and Translational Research, University of Pittsburgh*

Frank C. Sciurba, MD, *Professor, Division of Pulmonary, Allergy and Critical Care Medicine, University of Pittsburgh*

Clinton B. Wright, MD, *Director, Division of Clinical Research, National Institute of Neurological Diseases and Stroke (NINDS), NIH*

ACTIV-5

John Beigel, PhD, *Division of Microbiology and Infectious Diseases, NIAID, NIH*

OPERATION WARP SPEED

Tom Stock, DO, *Clinical Advisor to ACTIV-1 and Former Vice President, Clinical Development and Operations, Pfizer*

William Erhardt, MD, *Clinical Advisor to ACTIV-2 and Chief Executive Officer, Soundview Pharmaceutical Consultants*

Rachel Harrigan, MD, *Clinical Advisor to ACTIV-3 and Clinical Consultant for Drug Development and Former Head of Development Operations, Pfizer*

David Douglas, *Clinical Advisor to ACTIV-4 and Former Head, Global Research and Development Project Management Office, Pfizer*

Ciaran Lawlor, PhD, *OWS Consultant, Boston Consulting Group*

Gilbert "Lynn" Marks, MD, *Senior Adviser to BARDA, Office of the Director*

Sheri Parker, PMP, PhD, *CAPT, MSC, USN, Therapeutics Clinical Operations Director, Operation Warp Speed*

Ritika Philip, *OWS Consultant, Boston Consulting Group*

Col. Deydre Teyhen, *DPT, PhD*, *Director of Therapeutics, Operation Warp Speed*

TX-CLINICAL WORKING GROUP

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH (WG Co-chair)*

Stacey Adam, PhD, *Director, Cancer, Foundation for the NIH (FNIH)*

Helen Q. Chen, PhD, *Senior Consultant, Deloitte*

David Wholley, MPhil, *Senior Vice President of Research Partnerships, FNIH*

NATIONAL INSTITUTES OF HEALTH

Cynthia Boucher, *Clinical Trials Specialist, Division of Clinical Innovation, NCATS, NIH*

Tony Punturieri, MD, PhD, *Program Officer, Division of Lung Diseases, NIH, NHLBI*

STAFF

Evan Appell, *Consultant, Deloitte*

Dana Carluccio, PhD, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

From Judy to Everyone: 08:43 AM

I can send the list 20 sites coordinated by idPaz

do you have sites there

From Judith Hochman to Everyone: 08:56 AM

Strongly support this plan.

Action Items

- WG members to provide feedback on data categories for the inventories being created (1) preclinical compounds, (2) assays, (3) animal models, and (4) BSL-3/4 facilities.
- Subgroups to prioritize development of guidelines and frameworks to define use of animal models and in vitro assays to accelerate the 'path to clinic' of preclinical compounds

High-Level Meeting Summary

The ACTIV Therapeutics- Preclinical Working Group (WG) discussed and provided feedback on the updates from each of its two Subgroups—Animal Models and In Vitro Assays—after the Subgroups met this week.

The working group presented the data categories for the inventories being developed and requested feedback from the WG members.

Animal Models Subgroup Update

Small Animal Models

The hACE2 transgenic mouse model from Jackson Laboratory (JAX) holds promise for studying SARS-COV2. By June, JAX will be producing and making widely available approximately 1,000 mice per week. However, only 360 mice are now available, and only researchers conducting infectivity studies using the most promising compounds will have access. As more researchers use hACE2 mice to study COVID-19, they should deposit results in a shared database.

Researchers should also consider leveraging other animals such as Syrian golden hamsters, ferrets, and guinea pigs. Conducting multiple studies in parallel will facilitate rapid progress in identifying effective antivirals and using multiple animal species will allow for additional opportunities for discovery.

Using small animal models to test compounds against coronaviruses similar to SARS-COV-2 could improve future treatment of COVID-19 because the virus may change in unpredictable ways (e.g., by exhibiting seasonality). Researchers could also potentially leverage knowledge of how an existing compound acts *in vivo* against related coronaviruses to inform a safety protocol for SARS-COV-2 testing that will meet FDA approval. However, the co-chairs re-iterated the priority on focusing studies using SARS-COV-2.

It is essential to optimize immediately available animal models that can generate PK and toxicology data necessary to rapidly progress to clinical trials. Dr. Joseph Menetski proposed holding another Animal Models Subgroup meeting to establish a list of viable animal models for potential use by ACTIV.

Nonhuman Primate Models

Nonhuman primate (NHP) testing is currently hindered by two issues. First, the number of NHPs is insufficient for studying COVID-19 and establishing large enough colonies will require 2 to 3 years. Second, the number of Bio-Safety Level (BSL)-3 facilities, especially those capable of administering the aerosol tests necessary for studying airborne viruses, are limited.

Despite these limitations, NHPs are preferable to small animal models for testing immunomodulators and other late stage symptoms. Therefore, NHPs should be used exclusively for testing therapeutics to address COVID-19 late stage sympptoms. A list of NHP models and guidelines for running these models needs to be developed, as well as guidelines for prioritizing compounds for testing. NHP studies should be coordinated nationally, particularly for vaccine studies, which would be accelerated by a NHP master protocol. Running multiple tests simultaneously with a shared control arm would save time and use animal resources more efficiently. Reserving NHPs to test compounds with known PK and bioavailability information will help conserve resources. Finally, additional BSL-3 testing space needs to be created.

Data Sharing and Regulatory Issues

National Primate Research Centers and WHO's animal model working groups are currently sharing data. However, it will be necessary to form a central data repository for external groups to access and validate those data.

Regular communication with regulatory agencies will also help researchers progress rapidly. Developing a common Standard Operating Procedure outlining the best practices for testing animals using COVID-19-related therapeutics and vaccines will allow for efficient experimental designs that align with approval criteria. FDA plans to release guidance in the coming days regarding requirements for advancing compounds from preclinical to human testing.

In Vitro Assays Subgroup Update

Laboratories are currently running assays on different cell lines, which is powerful to validate a compound but suboptimal to compare compound efficacy among laboratories. ACTIV can solve this problem by identifying a list of preferred cell lines and making them widely available to researchers. ACTIV should also supply the research community with comparator compounds, such as Remdesivir, from a single source to ensure a common reference with established purity. By limiting the number of cell lines used for assays and providing reference compounds, ACTIV will ensure that laboratories around the world produce comparable efficacy results, which will accelerate the pace of drug discovery. ACTIV should also support laboratories by establishing a repository of cell lines to allow sharing of human cells, nonhuman cells, transgenic compounds, early stage viruses, and late stage viruses.

Facilitating Comparable Studies Across Laboratories

Many small research laboratories are beginning to test COVID-19-related compounds but may lack the level of drug development expertise found at large pharmaceutical companies. Therefore, ACTIV could suggest and publicize protocols to enable these small laboratories to conduct comparable studies to screen for efficacious compounds. ACTIV should also develop a list of suggested assays and characterize the strengths and limitations of each.

Skipping animal studies to advance compounds tested *in vitro* directly to human trials could be essential for rapid development of some types of COVID-19 therapeutics. It may be possible to test FDA-approved agents using a combination of cell cultures and organoids. If efficacy of these compounds is established *in vitro*, it may be possible to progress directly to human trials. However, this approach may only be possible with antiviral agents.

Appendix A: Participants List

WORKING GROUP MEMBERS

Annaliesa Anderson, PhD, *Vice President and CSO Bacterial Vaccines, Pfizer*

Kara Carter, PhD, *Senior Vice President Infectious Disease, Evotec*

Christine Colvis, PhD, *Director, Drug Development Partnership Programs, National Center for Advancing Translational Sciences (NCATS)*

Damon Deming, PhD, *Virologist, Division of Antiviral Products, Office of New Drugs, FDA, CDER, DAV*

Michael Diamond, MD, PhD, *Professor, Depts. of Medicine, Molecular Microbiology, Pathology & Immunology, Washington University School of Medicine*

Prabhavathi Fernandes, PhD, *Retired*

Greg Gatto, PhD, *Drug Development Regulatory Project Leader at RTI*

Jay Grobler, PhD, *Executive Director, Infectious Disease and Vaccines Discovery, Preclinical, and Early Development (DPED), Merck Research Laboratories*

Judy Hewitt, PhD, *Deputy Director, Office of Biodefense, Research Resources and Translational Research New Drugs, National Institute of Allergy and Infectious Diseases (NIAID)*

Samantha Jonson, MPS, *Special Assistant to the Director, NCATS*

Cat Lutz, PhD, *Senior Director, Mouse Repository & In Vivo Pharmacology, Rare and Orphan Disease Center, Jackson Laboratory*

Elizabeth Ottinger, PhD, *Project Manager, NCATS*

Srinivas Rao, MBA, PhD Global Head, Translational In Vivo Models Global Research Platform, Sanofi.

Jay Rappaport, PhD, *Director and Chief Academic Officer at Tulane Primate Center*

John Young, PhD, *Global Head Infectious Diseases and Early Development, Roche*

INVITED PARTICIPANTS

Christopher Austin, MD, *Director, NCATS*

Ken Duncan, PhD, *Deputy Director, Discovery: Therapeutics, Bill and Melinda Gates Foundation*

Ashley Parker, PhD, *Health Science Policy Analyst, NIH*

STAFF

Stacey Adam, PhD, *Science Program Manager at the Foundation for the NIH (FNIH)*

Joseph P. Menetski, PhD, *Associate VP of Research Partnerships, FNIH*

Rosa Alvarez, PhD, *Senior Consultant*, *Monitor, Deloitte*

David Frankowski, PhD*, Writer, Rose Li and Associates, Inc*

Appendix B: Chat Transcript

From Srinivas Rao to Everyone: 11:03 AM
Hi Everyone. My name is Srini Rao. I am with Sanofi...Nice to be here and meet all of you.

From Jay Grobler to Everyone: 11:15 AM
PK, route of administration, etc., will presumably be run in advance of advance of studies requiring BSL3 facilities to know whether the treatment studies will be provide useful data. Are we set with facilities for studies not requiring containment?

From Judy Hewitt to Everyone: 11:16 AM
I'm not aware of any issues. Would like to hear from others.

From annaliesa to Everyone: 11:18 AM
has there been discussion regarding using other coronaviruses for testing antiviral agents?

From Prabha to Everyone: 11:19 AM
Jay, glad you asked that. I have been pushing some PK before going into animal models Prabha

From Liz Ottinger to Everyone: 11:20 AM
I agree, could be included in SOPs, and what data is expected for PK

From Srinivas Rao to Everyone: 11:23 AM
for vaccine studies- potential ADE will be important to assess. important considering the papers on earlier SARS

From Jay Grobler to Everyone: 11:30 AM
DAAs have been advanced into the clinic for HIV, HCV without animal PoC data. Not strictly required. More relevant for host targets and immunological approaches.

From John Young to Everyone: 11:31 AM
Agreed. The issue of ADE was discussed at our meeting earlier next week.

From Judy Hewitt to Everyone: 11:47 AM
NIAID would happily accept cells/reagents in our (b)(4) repository for distribution to anyone, although to ship virus, they need to prove BSL-3 status. Protocols could be included. This takes distribution pressure off labs

From Judy Hewitt to Everyone: 12:04 PM
have to drop off for a clinical call, sorry

From Damon Deming to Everyone: 12:05 PM
Feel free to invite me to the subgroup discussions if you'd like feedback as to what might be (or under what conditions) expected from the FDA.